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Section of Odontology

President—ARTHUR BULLEID, F.D.S., L.R.C.P., M.R.C.S.

[*May* 24, 1954]

MEETING AT THE ROYAL COLLEGE OF SURGEONS, LINCOLN'S INN FIELDS, LONDON

COLYER PRIZE LECTURE

Malformations of the Teeth

By A. E. W. MILES, F.D.S., L.R.C.P., M.R.C.S.

Professor of Dental Pathology, London Hospital Medical College, Honorary Assistant to the Curator, Odontological Museum, Royal College of Surgeons

THIS is the first occasion on which the Colyer Prize has taken the form of a Lecture and I am deeply conscious of the honour that has been accorded me. It is indeed sad that on this particular occasion we are mourning the recent loss of Sir Frank Colyer to whom this lecture is intended as a tribute. During the course of his long and vigorous life of 87 years his immense energy and enthusiasm found expression in a succession of activities, his teaching, his practice, his writings and his war work; to each he brought a remarkable ability and virile intellect and through each he made important contributions to knowledge. There is little doubt, however, that of all these activities the Odontological Museum held for him the greatest attraction and it is certainly for us the greatest and most permanent memorial of his scientific achievement.

It is pertinent to note that the Colyer Prize is the result of a testimonial subscribed by Sir Frank's colleagues in recognition of his first twenty-five years' Curatorship of the Odontological Museum, a post to which he was appointed in 1900. At the time of his death, therefore, he had been in charge of this unique collection for more than half a century.

The Odontological Collection was originally brought together by the Odontological Society of Great Britain and was first housed in the Royal Dental Hospital of London. When in 1907 the old Odontological Society amalgamated with many other specialist societies to form the Royal Society of Medicine the Museum passed into the control of that newly formed Society. In 1909, three years before the Royal Society of Medicine moved to its present building in Wimpole Street, the Odontological Museum was transferred to the custody of the Royal College of Surgeons in Lincoln's Inn Fields where it came to form an integral part of the College Museum, though still strictly speaking remaining the property of the Royal Society of Medicine. The Odontological Section fortunately escaped the destruction by enemy action that befell the greater part of the College Museum during the last war and in 1943 the Royal Society of Medicine finally made a gift of its odontological specimens to the Royal College of Surgeons.

Under the care of Sir Frank Colyer the Odontological Museum has become one of the most important collections of odontological material in the world and is of immense value for teaching and research. In the Hunterian tradition and following the trend of Sir Frank's own inclination it is particularly rich in specimens of comparative anatomy, both normal and abnormal. With assiduous care he classified and examined this material and in 1936 the results of his studies were published in his monumental work "Variations and Diseases of the Teeth of Animals" (London). A later interest led to a fine collection of dental instruments and in 1952 to the publication of "Old Instruments Used for Extracting Teeth" (London and New York). These two publications have brought the Museum to the notice of a much wider public.

Sir Frank was greatly interested in malformations of the teeth and indeed did much to systematize these conditions. In consequence this field is richly represented in the Odontological Collection and forms a subject not inappropriate for a tribute to Sir Frank's memory.

Among the individuals of any species there is always a certain amount of variation, the relatively gross anatomical deviations from the normal being classed as malformations. The variety of malformations of the teeth is very great and only in certain instances have we any idea of the mode of reproduction or causation. Some are frankly hereditary and of genetic origin; others perhaps could be shown to be so if it were possible to examine other members of the families and undertake the laborious work of gathering the data for pedigrees. Trauma to a developing tooth germ can be

responsible for malformation of the definitive tooth and experimental work on animals and observations on man have established that if the region of the jaws is irradiated during the period of tooth development teeth may fail to develop or be dwarfed. The vast majority of dental malformations, however, appear to occur quite fortuitously and few writers have cared even to speculate on their ætiology. It is not possible in a short space to survey this subject comprehensively and it is therefore my intention to select but a few examples.

It is very common for the upper lateral incisors to be absent or reduced in size, either unilaterally or bilaterally, and the hereditary character of this feature has been demonstrated by many pedigrees, the most remarkable of which is that prepared by Jöhr (1934) who studied the population of an isolated Swiss village. About one-third of the population showed some degree of reduction of the lateral incisors and in a pedigree of enormous size Jöhr showed that the population was closely inbred and traceable back to a common ancestry at the beginning of the eighteenth century.

Anomalies of the lateral incisors have been described in families with a high incidence of cleft lip and it has been suggested that they represent minor degrees or "formes frustes" of the same disturbance of development. Before this view could be accepted it would be necessary to show that the incidence of lateral incisor anomalies is consistently higher in such families than in the general population. It is of interest that whereas cleft lip is significantly more common on the left side Brekhus and his colleagues (1944) found that in otherwise normal persons the right lateral incisor was absent slightly more frequently than the left, although peg-shaped lateral incisors were more common on the left side.

The frequency with which lateral incisors of the upper jaw, and third molars of both jaws, are absent has been interpreted as evidence of an evolutionary trend towards the numerical reduction of the dentition of man, associated with a progressive shortening of the jaws. There is little doubt that there has been some evolutionary modification of the size of the jaws and of the general characteristics of the dentition of man but it is very doubtful whether any powerful influences are active which are likely to lead to a reduction in the number of teeth in the future, however beneficial to the welfare of man such a reduction might be. The evolution of man's dentition, like that of his physical constitution in general, is very difficult to predict as the process of natural selection hardly affects civilized man in the same way as it affects other animals.

Absence of teeth may be part of a generalized ectodermal hypoplasia or dysplasia affecting the skin and its appendages, the hair, nails, sweat glands, and very rarely the salivary and lacrimal glands. These conditions are usually hereditary and, although it is commonly stated that two modes of inheritance occur, one being sex-linked recessive and the other irregularly dominant, it is probable that at least in some families a more complex genetic mechanism is involved (Helwig-Larsen and Ludvigsen, 1946).

Ellis and Van Creveld (1940) described three unrelated children in whom ectodermal dysplasia with absence of teeth, polydactyly and achondroplasia occurred in association. Two of the children also had a congenital heart lesion and two were the offspring of first-cousin marriages. Other cases have since been reported by Weller (1951) and Caffey (1952). According to Ellis and Van Creveld the association of the four congenital abnormalities, ectodermal dysplasia, polydactyly, achondroplasia and congenital heart disease, constitutes a distinct syndrome. Miller (1937) and Willner (1936) have each described patients in whom absence of teeth, achondroplasia and polydactyly were associated, and Fackenheim (1888) described a family in which absence of teeth was associated with polydactyly alone. It is possible that these cases represent incomplete examples of what has been called the Ellis-Van Creveld syndrome.

Malformation of the iris (Mathis, 1936), deformed hands and feet (Berendt, 1948) and microglossia (Dockrell, 1950) have been described in association with the absence of many teeth and a family has been reported by Böök (1950) in many members of which absence of several premolars was associated with early greying of the hair. Most of the affected persons also had hyperhidrosis of the palms of the hands and soles of the feet. Calnan (1949) and Rushton (1953) have each described a child with congenital hypoplasia of one side of the body and absence of many teeth, especially on the affected side. The father of Calnan's patient suffered from shingles shortly after the estimated date of conception and Calnan suggests that it is possible that the male germ plasm was affected by the virus of herpes zoster.

A number of cases of excessive hairiness associated with absence of teeth appear in the literature. Most were recorded before X-rays were in common use and none of the cases described is really convincing. It is possible that at least some were due to interference with eruption by congenital gingival hyperplasia which is known to be associated sometimes with hirsuties.

Supernumerary teeth are common, especially in the incisor region of the upper jaw. If they are of the tuberculate variety (Fig. 1) the crowns frequently have deep enamel invaginations. Sir Frank Colyer was probably the first to draw attention to this (Colyer, 1926). Supernumerary teeth usually develop more or less synchronously with the adjacent teeth but occasionally their development is out of step with that of the rest of the dentition (Figs. 1, 2 and 3). Supernumerary teeth in the deciduous dentition are sometimes but not always succeeded by corresponding teeth in the permanent dentition (Fig. 4).

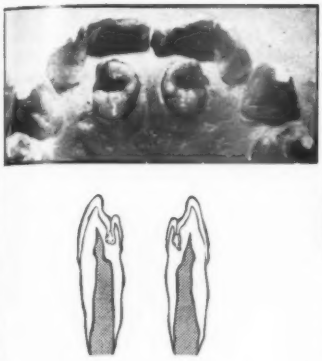


FIG. 1.—Age 13. Tuberculate supernumerary teeth erupted behind the central incisors. The diagram shows labio-lingual sections through the supernumeraries drawn from radiographs of the specimens and shows that each has an enamel invagination leading from the central fossa of the crown. Although the apices of all the teeth in the region would have been fully formed at this age, those of the supernumeraries are widely open and incompletely formed.

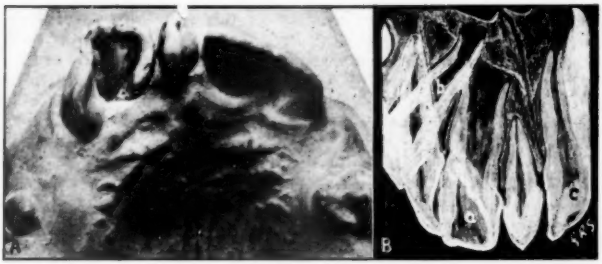


FIG. 2.—Boy aged 11 years with two erupted supernumerary teeth in the upper incisor region. A, Model showing a median simple conical tooth. The other supernumerary in the position of the right central incisor is of distorted incisor form. B, Drawing from radiograph. Note the asynchrony between the stages of development of the roots of the supernumeraries, the root of the conical one being complete and that of the other (a) incomplete. The apical foramen of the misplaced central incisor (b) is also widely open in comparison with that of the opposite side (c).

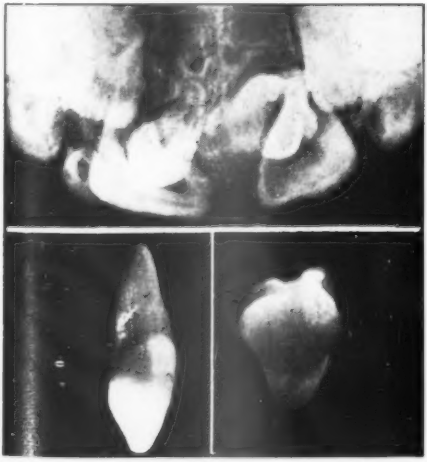


FIG. 3.—Girl aged 6½ years. Unerupted supernumerary teeth on palatal aspects of the upper permanent central incisors. On the right side the supernumerary is conical and on the left side tuberculate with a cruciform incisive edge. The apices of both supernumeraries were complete whereas the roots of the permanent incisors were incomplete.

FIG. 4.—Boy aged 5 years. Radiograph showing an erupted supernumerary deciduous tooth in the right lateral incisor region, with a developing successor associated with the permanent dentition.

Most supernumerary teeth seem to occur fortuitously but there are records of supernumeraries appearing in more than one member of a family. Farrar (1888), for example, described a girl with a conical supernumerary in the palate behind a central incisor. Webster (1927), thirty-nine years later,

reported that two of the children of this same girl each developed a supernumerary in the same situation. Opportunity seldom occurs for a follow-up over such a very long period but it is only by such careful recording that we can hope to learn something of the familial incidence of these conditions. The occurrence of multiple supernumerary teeth is a feature of familial cleido-cranial dysostosis.

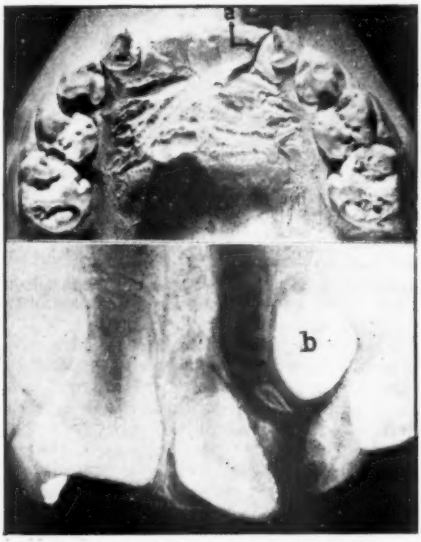


FIG. 5.—Boy aged 4 years. Cleft of alveolar process associated with cleft lip, operated upon at three weeks. A, Model showing cleft (a), on lateral side of which is a "precanine" with the morphology of a lateral incisor and very slightly smaller than the lateral incisor of the opposite side. A A and a supernumerary tooth on the medial side of the cleft have been extracted. B, Radiograph showing that the "precanine" has a successor (b). There is a minute conical tooth in the cleft.

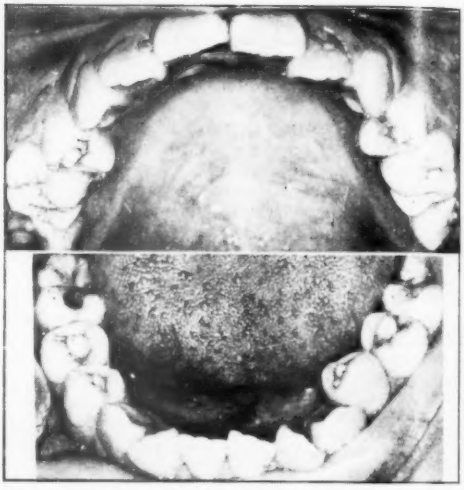
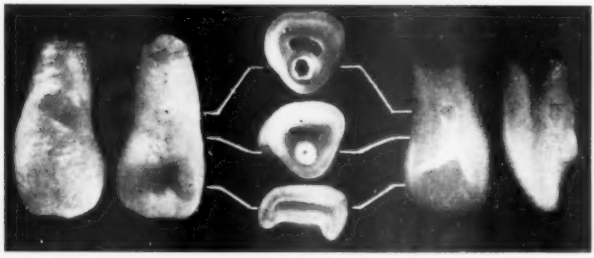


FIG. 7.—Enamel covered projections on the occlusal surfaces of the premolars of a 16-year-old Chinese girl.



A B C D E

FIG. 6.—Girl aged 8½ years. Left upper lateral incisor of well-marked shovel form with enamel invagination. A, Labial view. B, Lingual view. C, Transverse ground surfaces at different levels. D, Radiograph from lingual aspect. E, Lateral radiograph. The root is not yet fully formed.

Supernumerary teeth commonly develop in the region of the cleft in cleft lip. A tooth, the so-called pre-canine, is frequently present medial to the canine on the lateral side of the cleft. These supernumeraries sometimes have the form of normal lateral incisors (Fig. 5) and the problem of how an incisor comes to develop in what appears to be the maxillary process has given rise to a very interesting literature. According to Lannelongue and Ménard (1891), the lateral incisors normally develop

from two components ; a medial one which develops in the fronto-nasal process and a lateral one which develops in the maxillary process. In developmental clefts in this region the fronto-nasal and maxillary processes fail to unite and according to Lannelongue and Ménard the two components of the lateral incisor either give rise to separate teeth or one or both of them fail to develop.

It has often been suggested that supernumerary teeth are examples of atavism, or the reappearance of teeth possessed by a remote ancestor of man. A simple concept of atavism is to-day in general discredited by embryologists (de Beer, 1940) and it seems that supernumerary teeth in man should be interpreted as an instance of the widespread phenomenon of organ reduplication; comparable in fact with polydactyly where, since the remote ancestors of man did not possess more than five digits on each extremity, the question of atavism does not arise.

A malformation which has received a good deal of attention recently (Hallett, 1953) is the enamel invagination observed most commonly on the lingual surfaces of the crowns of upper lateral incisors. This condition seems to be common in teeth with crowns of shovel form with a prominent cingulum and prominent mesial and distal marginal ridges on the lingual aspect (Fig. 6), and also in the variation of the lateral incisor in which there is a concavity on the mesial surface of the crown near the cervix. According to Atkinson (1943) depressions on the mesial surfaces of the crowns of lateral incisors and also enamel invaginations are due to compression of the tooth germ during development. He points out that the formation of this tooth often does not commence until long after that of the central incisor and canine and, in consequence, the lateral incisor has little space in which to develop. Enamel invaginations, however, appear to be closely related to, and indeed to be minor degrees of, dens in dente, in which the tooth is often dilated rather than compressed. This suggests that Atkinson's view is incorrect.

Tratman (1949, 1950) has described in Chinese people a very curious anomaly consisting of small enamel-covered projections near the centres of the crowns of the premolars. Fig. 7 shows an example. The projection on the lower left second premolar extended well above the level of the buccal cusp and broke off exposing a slender prolongation of the pulp. Pedersen (1949) has described similar "enamel pearls" on the crowns of maxillary canines and premolars in Eskimos.

Herbst and Apffelstaedt (1930) have described a very rare malformation known as "odontocele" in which a mass of dentine uncovered by enamel protrudes from the crown of a tooth and which they attribute to trauma during development. Schour and Kronfeld (1938) described an example in a child of 7 months who died from a severe intracranial birth injury. Sections through the upper jaw (Fig. 8) showed that at the middle of the occlusal surfaces of the second deciduous molars of both

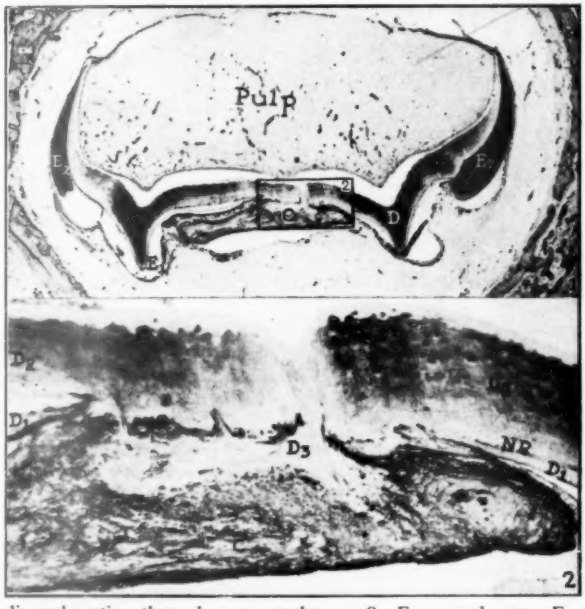


Fig. 8.—1, Bucco-lingual section through upper molar. × 9. E_1 enamel space, E_2 postnatal enamel, D dentine, O odontocele. 2, Higher magnification of the odontocele in area 2. × 46. D_1 prenatal dentine, D_2 postnatal dentine, NR neonatal line, D_3 mushroom-like mass of dentine, C irregular calcified tissue. (With acknowledgments to A.M.A., *Arch. Path.*—Schour and Kronfeld (1938) **26**, 485.)

sides there was a mushroom-like mass of dentine which could only have been formed by a herniation of part of the dentine papilla through the occlusal surface. As pointed out by Schour and Krogfeld, the lesions could be related to the time of birth by their relation to the prominent incremental line, the neonatal line, in the adjacent dentine (Fig. 8), and were no doubt due to crushing of the tooth germs at birth when little more than the tips of the cusps were formed.

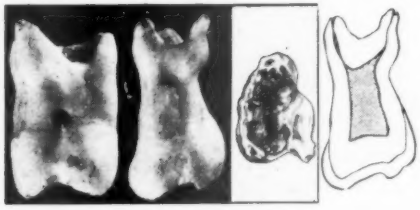


FIG. 9.—Upper left molar from modern European showing marked taurodontism. The stem of the root is prismatic and ends in three short rootlets between which the apical surface is concave. × 1·25. A, Distal surface. B, Buccal surface. C, Drawing of apical surface. D, Diagrammatic representation of mesio-distal section drawn from radiograph, showing large pulp chamber extending into the stem of the root.

Fig. 9 shows a rare abnormality which resembles very closely indeed a condition of the roots found in Krapina and other examples of Neanderthal man and for which the term taurodontism was coined by Sir Arthur Keith. In this condition the roots are prismatic or cylindrical and only bifurcate at the extremity or the extremity may end abruptly in a flat or, as in the present example, concave surface, rather like the pressed-in bottom of a wine bottle. The other characteristic is the large pulp cavity extending well into the root.

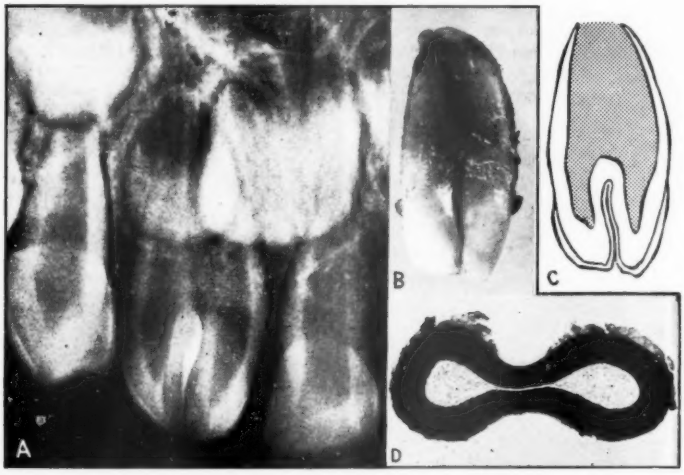
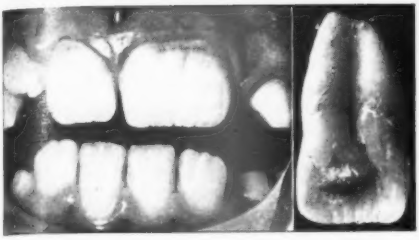


FIG. 10.—Boy aged 3 years. Double tooth consisting of deciduous lateral incisor and a supernumerary element. The root portions only are joined. A, Radiograph showing normal lateral incisor in the developing permanent dentition. B, Labial view of specimen. C, Diagram representing mesio-distal section drawn from radiograph of the specimen. D, Transverse section through the root showing common pulp cavity. × 7·5.

There is a variety of tooth anomaly, depicted in Figs. 10, 11, 12, 13 and 15, which bears evidence of being composed of two or more teeth or parts of teeth and for which terms such as gemination, incomplete dichotomy, synodonty and odontopagy have been employed. The choice of terms depends mainly on which of two divergent views of the origin of what may perhaps be called most simply "double teeth" is supported. According to one view double teeth result from a process of fusion or joining up of tooth germs while according to the other they result from a process of partial splitting or dichotomy of a tooth germ. Insufficient evidence is available to determine this question but there are a few observations which may be significant. Sir Frank Colyer (1944) described a number of



A B

FIG. 11.—Boy aged 9 years. A, Very wide central incisor on the left side. The left lateral incisor was present but unerupted. B, Lingual view of specimen showing evidence of double origin. The pulp cavity was single.

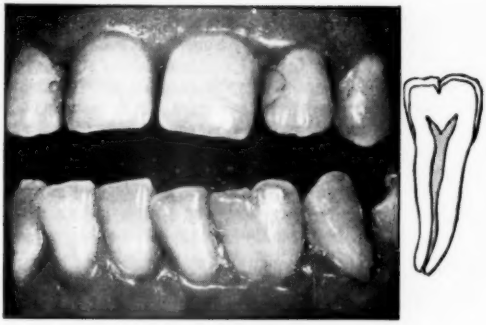


FIG. 12.—Woman aged 32 years with a double tooth involving a lower lateral incisor and a supernumerary element. There was syndactyly of the second and third toes of both feet and her male infant had a similar malformation of the feet and also a harelip on the left side. The association of these malformations may have been fortuitous.

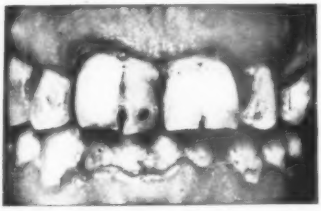


FIG. 13.—Male aged 38 years. Large upper central incisors with evidence of double origin. Other members of the family were similarly affected, either having notched or very large central incisors (Fig. 14).

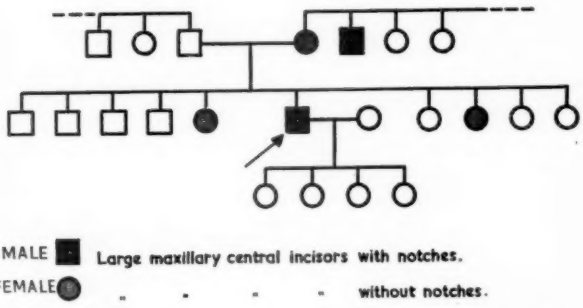
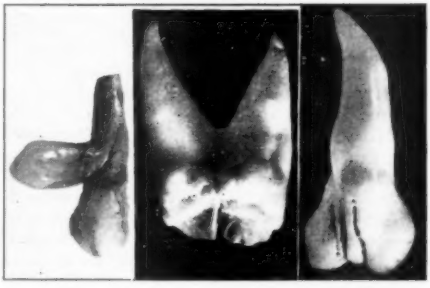


FIG. 14.—Pedigree of man, indicated by arrow, whose teeth are depicted in Fig. 13.



A B C

FIG. 15.—A, Double tooth comprising an upper premolar and an additional element with a simple conical crown. B, Double tooth comprising two upper permanent incisors, probably a lateral incisor and supplemental tooth. This is a very unusual specimen because the crowns are united but the greater parts of the roots are separate. The enamel of the crowns is markedly hypoplastic. C, Left upper permanent canine the crown of which consists of two joined elements. The tissue at the site of fusion is raised into folds producing an appearance suggestive of distortion by pressure.

examples of bundles of small tusks in place of a single tusk in elephants and attributed the condition to traumatic injuries. The work of Glasstone (1952), who found that each half of rabbit molar tooth germs cut in two formed a rudimentary whole tooth when grown in tissue culture, is also perhaps significant in connexion with the origin of both double teeth and supernumerary teeth.

It will be noted that the examples depicted, with the exception of Fig. 15B, show various degrees of separation of the crowns whereas the roots are single. This is almost invariably the case and specimens with joined crowns and separate roots (Fig. 15B) are very rare indeed. Since it is the tips of the crowns that are formed first this means that in the initial stages of development of the majority of double teeth the elements must have had separate identities and union could only have occurred as development proceeded. This observation would appear to be more consistent with the theory of fusion rather than that of dichotomy.

Euler (1939) described a specimen which he considered afforded some support for the fusion theory of the origin of double teeth. In his specimen there was a ridge of tissue at the point of junction of the two elements producing an appearance suggestive of distortion by pressure. A specimen of similar character is depicted in Fig. 15C but without histological examination it is not possible to interpret this unusual feature with any degree of certainty.

Studies of identical twins are of great significance in helping to distinguish anomalies which are of genetic origin from those which are due to non-genetic disturbances of development. "The frequency of concurrent appearance of a trait in both members of pairs of one-egg twins provides an estimate of the extent to which a given trait is hereditary" (Lasker, 1947). It must be borne in mind that identical twins may be inversely symmetrical or "mirror images" of one another.

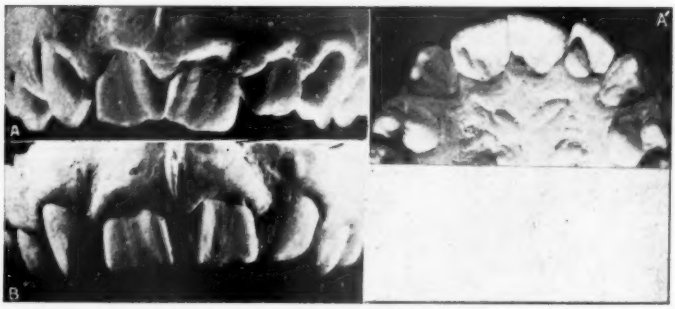


FIG. 16.—Models of female identical twins (A, A′ and B) aged 18 years, showing concordance in tooth morphology and discordance in other respects.

Fig. 16 shows the anterior teeth of a pair of female twins who were undoubtedly identical; apart from a close physical resemblance a detailed examination of their blood groupings showed that they possessed ten identical red cell antigens. The morphology of their upper central incisors, which were of distinctive character, was strikingly similar; the mesial margin of the labial surface was raised to form a prominent vertical ridge. In both twins on the right side the upper lateral incisor was absent. On the left side in one twin (Fig. 16, A, A′) the lateral incisor was present but it was malformed with a pointed cusp on the lingual aspect arising from the cingulum. In the other twin (Fig. 16, B) the left lateral was absent and there was in that region an inclusion or globulo-maxillary cyst. It is possible to postulate that there was in both twins some disturbance of development in the left lateral incisor region, in one merely giving rise to an additional cusp, in the other leading to total failure of the tooth to develop and to the formation of a developmental or inclusion cyst. This led to some discordance between the twins in this region in contrast to the striking concordance in other respects.

In spite of the various mechanisms which protect the embryo from environmental changes, the susceptible developing tissues are at times exposed to noxious influences which interfere with the complex process of development and much evidence has accumulated in recent years to show that embryonic damage due to influences of this kind may be responsible for many types of congenital malformation. Maternal infection with micro-organisms and viruses, rhesus factor incompatibility (Wiener, 1946), dietary deficiencies of vitamins (Giroud, 1954) and mineral salts, irradiation of the maternal pelvis during pregnancy and the maternal administration of cortisone (Frazer *et al.*, 1953) and of toxic substances such as trypan blue have all been shown to produce more or less specific disturbances of development in the offspring (Warkany, 1947; Boyd and Hamilton, 1950). Much of the evidence, but not all, relates to laboratory mammals and is only indirectly applicable to the problem of malformations in man and even more indirectly still to the problem of the causation of dental malformations. It is of special interest that not all strains of laboratory animals are equally susceptible to environmentally induced developmental abnormalities (Frazer *et al.*, 1953; Giroud,

1954) so that it is possible that at least some examples of aberrant development result from a combination of both genetic and non-genetic factors.

It is well known, of course, that infection of the fœtus of a syphilitic mother produces a characteristic malformation of the teeth. The fœtus is not infected until a relatively late stage of the pregnancy, as is exemplified by the fact that the deciduous teeth are never affected, because in the earlier stages the placental barrier is effective against the passage of the *Treponema pallidum* (Hoffmann, 1936).

In laboratory animals maternal vitamin deficiencies, too slight to produce signs of avitaminosis in the parent animals, have been shown to cause many types of malformation in the offspring (Giroud, 1954). Warkany and Nelson (1941) noted skeletal abnormalities, especially shortness of the tooth-bearing portion of the mandible, in the offspring of rats reared on riboflavin-deficient diets, and it is noteworthy that in some instances the mandibular incisors were absent (Warkany, 1954).

It is now well established that even mild attacks of rubella during the first few months of pregnancy are liable to produce developmental abnormalities in the infant. Cataract, deaf-mutism and cardiac anomalies are the most common abnormalities but cleft palate, mental deficiency and mongolism have also been reported. There is less good evidence that other virus infections, such as influenza and mumps, may be responsible for fœtal damage. Interest in maternal rubella from the dental point of view arises from the fact that here and there in the now extensive literature on the subject appear ill-defined references to delayed eruption, malformed teeth and absence of teeth. Hagelsteen (1946) described an infant with a deformity of the face which appeared to be due to absence of the zygomatic arches; the mother had rubella at an early stage of pregnancy. Krause (1945) referred to "dental aplasia" in a rubella infant. Abel and Van Dellen (1949) included "malformed teeth" among the abnormalities present in 5 out of 81 babies whose mothers had rubella during pregnancy, and an unspecified tooth anomaly is referred to in a similar study made by Grönvall and Selander (1948). Patrick (1948) noted mild enamel hypoplasia of the deciduous teeth in 3 out of 24, and retardation of the eruption of the first permanent molars in a larger proportion, of blind or deaf children with a history of maternal rubella. Gunther (1952), in what appears to be an important paper although only an abstract is available to me, says that rickets commonly develops in children with "embryopathia rubeolosa" and that the dentition is late in appearing. Retarded eruption has also been noted by Gregg and his colleagues (1945) and by Clayton-Jones (1947).

The only clinical studies that throw any light on the exact nature of the dental anomalies are those of Evans (1944, 1947) who examined 67 young children with various malformations attributed to maternal rubella. In 6 children there was marked retardation of tooth eruption, the first tooth, which in 2 cases was a second molar, appearing at between 12 and 24 months; in 1 child both lower deciduous lateral incisors were absent and in 2 others an upper lateral incisor was absent; in 13 children there were various degrees of enamel hypoplasia, including severe degrees that are rare in random groups of children. Although Evans has not described the enamel lesions in great detail, it appears that at least in many instances enamel formed before birth was affected.

Delayed eruption in infants affected by maternal rubella may well be secondary to nutritional deficiencies during the first few months after birth because such infants present serious feeding problems and are extremely difficult to rear.

Substance is added to the rather imprecise clinical accounts of dental malformations in association with the prenatal rubella syndrome by observations made by Stocker (1951) who examined serial sections of the jaws of a one-month premature infant of a mother who had rubella at the end of the sixth week of pregnancy. There was complete absence of all the permanent tooth germs and marked degenerative changes in the enamel organs of the deciduous teeth of a kind which would no doubt have resulted in hypoplastic defects of the definitive teeth (*see also* Töndury, 1953). It may be mentioned that Stocker described enamel invaginations in the crowns of the developing maxillary canines.

Dental anomalies are common in mental deficiency and especially in mongolism—conditions which are in the nature of abnormal development. Spitzer and Mann (1950) have noted an association between mental deficiency, lens defects, enamel hypoplasia of the permanent dentition and, less frequently, absence of teeth and microdontia, and attribute these to a common cause. They point out that all the affected tissues are of ectodermal origin and that the syndrome could be explained on the basis of a defect of that germ layer. The maternal and family histories of most of the people studied, who were between the ages of 19 and 64 years, were unknown and the cause of the postulated ectodermal defect must remain a subject of speculation. Spitzer and Mann point out that many of the lenticular lesions were different from and less severe than those described in the rubella syndrome. It would seem possible that the enamel hypoplasia of the permanent teeth was due to post-natal nutritional deficiencies associated with difficulties of feeding mentally deficient infants.

Recent advances in knowledge have led to a better appreciation of the causes of faulty development and have thrown a glimmer of light on the problem of dental anomalies. It is manifest that this is a field in which careful clinical observation and recording, as well as experimental research, are needed in order to advance our knowledge still further, and, in particular, to define more clearly the parts played by genetic and environmental causes in the origin of dental defects.

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Section of Experimental Medicine and Therapeutics

President—G. A. H. BUTTLE, O.B.E., M.A., M.R.C.S., L.R.C.P.

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DISCUSSION: THE SERUM PROTEINS

Dr. F. V. Flynn (Department of Clinical Pathology, University College Hospital, London):

Electrophoretic Patterns of the Serum Proteins in Health and Disease

The term electrophoresis refers to the migration of charged particles in an electric field. When serum protein is exposed to the influence of an electric field, under certain specific conditions, the proteins fractionate into groups of differing mobility—each group migrating towards one of the electrodes at a different velocity. The number of fractions that can be distinguished depends particularly on the species of animal from which the serum is derived and on the pH and ionic concentration of the suspending medium.

For the large majority of workers electrophoretic analysis of the proteins has remained until recently an unobtainable luxury, as the apparatus required for the classical Tiselius procedure is too costly, bulky and complex. The advent of the method of paper electrophoresis, introduced by Wieland and Fischer (1948)[1], Durrum (1950)[1], and Cremer and Tiselius (1950)[1], has entirely changed this state of affairs by placing electrophoretic analysis within the scope of even small laboratories.

Although introduced but a few years ago, paper electrophoresis now has quite a considerable literature of its own; by the middle of 1953 there were some 70 papers dealing with the subject, but nearly all of these have been concerned with method. A few papers have been mainly devoted to interpretation of results and include those of Brante (1952), Slater and Kunkel (1953), Griffiths and Brews (1953), Squire (1953), Antonini and Piva (1953), and Paton *et al.* (1954).

In the department of Clinical Pathology at University College Hospital, in collaboration with Mr. P. de Mayo, Mr. A. J. Cummings and Dr. Ann Warrick, I have examined many hundreds of sera by paper electrophoresis, and examples of important changes found in the electrophoretic pattern in health and disease are illustrated in this communication. The results obtained by paper electrophoresis can be put on a quantitative basis, but here results obtained by a qualitative technique are shown. In practice we have found that adequate information for routine clinical work can be obtained by simple visual assessment of the paper strip, provided the technique is properly standardized. The importance of studying the form of the protein spectrum cannot be over-emphasized, for information of diagnostic significance may be present there which is not conveyed in purely quantitative data.

METHOD

We have continued to use a method previously described (Flynn and de Mayo, 1951). A strip of Whatman No. 1 filter paper is supported in a special tank with its ends dipping into electrode compartments which contain a large volume of a barbiturate buffer of pH 8·6 and ionic strength 0·1. The paper is allowed to become saturated by capillarity and when the system is in equilibrium 15 microlitres of fresh non-hæmolysed serum is evenly applied in a thin line at the apex of the paper. A direct current at a potential of 110 volts is then applied for about sixteen hours. This causes the negatively charged protein particles to migrate towards the positive pole and the fractions to separate. The separated protein fractions are fixed to the paper by heat coagulation and subsequently stained by immersion in a solution of Naphthalene Black, a protein-staining dye. Excess dye is then washed off the paper.

The intensity of the colour of the stained protein bands reflects the concentration of the individual protein fractions.

THE ELECTROPHORETIC PATTERN OF THE SERUM PROTEINS IN HEALTH

(1) *The pattern in the normal adult.*—Fig. A, 1–3 shows the pattern obtained with serum and plasma. The serum shows 5 bands and the plasma an additional fibrinogen band, which is situated at the

point where the plasma was originally applied to the paper, in a position between the γ and β globulins. As this region of the electrophoretic spectrum is often of great importance from the point of view of diagnosis, we use serum in preference to plasma for routine analyses. In the absence of a fibrinogen band interpretation is much easier.

In the normal adult pattern it should be noted that albumin forms the densest band, and also—taking both colour intensity and band width into consideration—that the γ globulin band retains slightly more dye than the β globulin, which in its turn retains slightly more dye than the α_2 globulin. The α_1 globulin is normally only just discernible as a distinct band. The normal range of concentration for the various protein fractions is fairly wide, especially for the γ and α_1 fractions and this must be borne in mind when interpreting patterns from patients.

(2) *The pattern in normal infants.*—We have studied the pattern in a small number of normal infants, and typical results are shown in Fig. B, 1–3. The pattern in infancy differs somewhat from that found in the normal adult and varies significantly with age. The α_2 globulin concentration is high in infancy, increasing markedly shortly after birth, and it falls steadily with increasing age. The β globulin sometimes shows similar changes. The γ globulin concentration at birth is a little higher in the fœtal than maternal blood, but it falls thereafter to reach its lowest level between two and six months. The normal adult level is reached by 5–11 years.

(3) *The pattern in pregnancy.*—In pregnancy the pattern shows a significant variation (Fig. C, 1–3). The serum albumin concentration falls during the second three months and remains low until delivery. The α_1, α_2 and β globulins begin to increase during the second trimester and the changes become marked in the last three months. The γ globulin concentration falls slightly as the other globulin fractions increase. In toxæmia we have found that these changes are accentuated. The pattern returns to normal by two to three months postpartum.

The Electrophoretic Pattern of the Serum Proteins in Pathological States

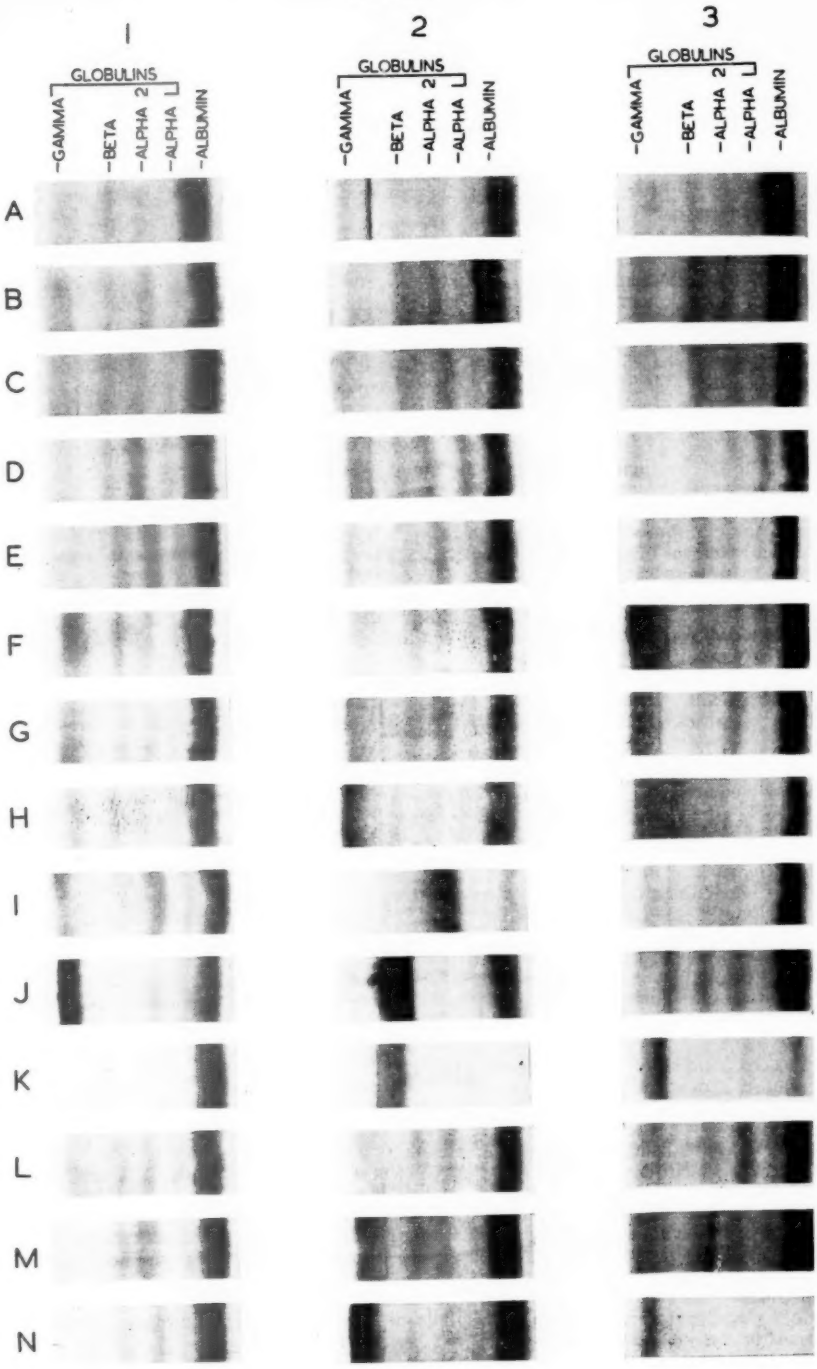
(1) *The pattern in non-bacterial tissue injury.*—In Fig. D, 1–3 the changes we have found in a few cases are shown. When tissue necrosis occurs increase of the α globulins may often be observed, and the increase may be marked within a few days. Acute hepatic necrosis, however, appears to provide an exception to this finding.

(2) *The pattern in acute infections.*—The characteristic findings in acute infections are increase of the α globulins during the acute stage, and increase of the γ globulin in the late stage and during

Key to Plate I

A.	Normal adult		
	1. Serum	2. Plasma	3. Serum
B.	Normal infant		
	1. Newborn	2. 8 months	3. 14 months
C.	Pregnancy		
	1. Early	2. Middle	3. Late
D.	Non-bacterial tissue injury		
	1. Coronary thrombosis	2. Fracture of femur	3. Irradiation
E.	Acute infection		
	1. Rheumatic fever	2. Lobar pneumonia	3. Empyema
F.	Chronic infection		
	1. Subacute bacterial endocarditis	2. Pulmonary tuberculosis	3. Kala-azar
G.	Collagen disease		
	1. Disseminated lupus erythematosus	2. Polyarteritis nodosa	3. Rheumatoid arthritis
H.	Liver disease		
	1. Infective hepatitis	2. Acute hepatic necrosis	3. Cirrhosis
I.	Kidney disease		
	1. Acute nephritis	2. Nephrotic syndrome	3. Chronic nephritis
J.	Multiple myeloma		
	1. γ-myeloma	2. β-myeloma	3. M-myeloma
K.	Urine patterns		
	1. Acute nephritis	2. Multiple myeloma	3. Multiple myeloma
L.	Malignant disease		
	1. Carcinoma of bronchus	2. Hodgkin's disease	3. Carcinoma of thyroid
M.	Miscellaneous conditions		
	1. Cushing's syndrome	2. Sarcoidosis	3. Primary xanthomatosis
N.	Rare protein disorders		
	1. Agammaglobulinæmia	2. Macroglobulinæmia	3. Cryoglobulinæmia

PLATE I


1
2
3
GLOBULINS
GLOBULINS
GLOBULINS
GAMMA
BETA
ALPHA 2
ALPHA
ALBUMIN
A
B
C
D
E
F
G
H
I
J
K
L
M
N

convalescence (Fig. E, 1–3). The extent of the rise of the α globulins can be roughly correlated with the height of the temperature, and the increase may be obvious within a few days. The changes take several weeks to return to normal, after the onset of the condition.

(3) *The pattern in chronic infections.*—The notable finding in chronic infections is increase of the γ globulin. In addition there may be increase of the α globulins in more active infections (Fig. F, 1–3). Generally the more chronic the infection the higher the γ globulin. In tuberculosis, however, the γ globulin may be normal.

(4) *The pattern in collagen diseases.*—The most notable and consistent feature, even in the early stages, is a considerable increase of the γ globulin. In addition, increase of the α_2 globulin is found in almost all cases and increase of the α_1 globulin and diminution of the albumin are often found (Fig. G, 1–3).

(5) *The pattern in liver disease.*—In liver disease the characteristic features are a large increase of the γ globulin and diminution of the serum albumin. The extent of the abnormality, especially diminution of the albumin, appears to depend on the severity and the duration of the disease process, but even with local lesions in the liver, e.g. metastases, the γ globulin may be increased. Sometimes the β globulin is raised when there is increase of the serum lipids, but usually the fractions other than the γ globulin and albumin show only small changes (Fig. H, 1–3).

In viral hepatitis the γ globulin is usually only slightly or moderately increased; in the early stage it may be normal and in some cases with negative flocculation tests it remains so. Usually the γ globulin is maximal in the second week after the onset of symptoms, but in cases going on to chronic hepatitis and cirrhosis the γ globulin continues to rise for months. The α globulins are increased in most cases but the β globulin is not frequently raised. The albumin only shows marked and obvious diminution in cases which have become chronic.

In massive hepatic necrosis the pattern is very unusual and would appear to be diagnostic, with marked diminution of the α globulins and sometimes also the β globulin. We have seen a pattern similar to the one illustrated in 3 cases of acute hepatic necrosis. Presumably the decrease of the albumin and increase of the γ globulin reflect the existence of hepatitis for some time prior to the onset of massive necrosis.

In cirrhosis the pattern is often diagnostic, with a large diffuse increase of the γ globulin which tends to link up with the β globulin as a result of increase of the faster moving γ globulins. This leads to absence of the usual pale area between the γ and β globulin bands. We have noted this in all types of cirrhosis in just over half the cases. The γ globulin sometimes shows an enormous increase, particularly in cases in which previous attacks of viral hepatitis can be elicited in the history. The serum albumin is usually markedly reduced, particularly so in cases with ascites. The α globulins are increased in less than half the cases. The β globulin is notably raised in cases of biliary cirrhosis.

(6) *The pattern in kidney disease.*—The pattern differs with different clinical syndromes as shown in Fig. I, 1–3.

In acute glomerulonephritis, Ellis Type I, the albumin is slightly reduced and usually the γ and α globulins are increased.

In cases of the nephrotic syndrome the pattern is quite diagnostic with marked diminution of the albumin, tremendous increase of the α_2 globulin, and in the vast majority of cases diminution of the γ globulin. In addition diminution of the α_1 globulin is often found and there may be a small increase of the β globulin. In about half the cases the α_2 and β globulins fail to resolve completely. The extent of the changes correlates well with the clinical severity, but in children the changes are more gross than in adults. In chronic nephritis the pattern differs little from normal except for some diminution of the serum albumin and some increase of the α_2 globulin. In cases of kidney disease electrophoresis of the urine protein shows, in addition to albumin, the presence of significant amounts of globulins, with often β and α_1 fractions showing preferential excretion.

(7) *The pattern in myelomatosis.*—In myeloma electrophoresis has its greatest diagnostic value. Where electrophoresis of both serum and urine protein is carried out the result will be diagnostic in more than 95% of cases.

The types of diagnostic serum pattern are illustrated in Fig. J, 1–3. The diagnostic feature of these patterns is the occurrence of an abnormal *compact* band somewhere on or between the γ and β positions: most frequently the band is somewhere on the γ position. Often the concentration of the abnormal protein is very high, giving a particularly dense band, but this is not necessarily so: indeed, the strip may reveal the presence of a myeloma globulin when the total globulin figure is quite normal. In addition to the presence of a myeloma globulin, other changes usually found are diminution of the serum albumin and increase of α globulins. Often the concentration of the normal γ and β globulin is diminished. An important question is the specificity of the finding of a compact narrow band: we have found such a band in the serum from a proved case of macroglobulinæmia, in two cases of obscure anæmia in which no satisfactory diagnosis has yet been made, and as a transitory phenomenon in a simple case of the nephrotic syndrome. However these are the only exceptions in many hundreds of sera.

Examination of the urine protein, after preliminary concentration if necessary, is extremely valuable and should be carried out whether the ordinary heat test for Bence-Jones protein is positive or not. The urine pattern may be diagnostic of myeloma when the serum pattern is equivocal. Examples of diagnostic patterns are shown in Fig. K, 1–3. A predominant protein band is found on or between the γ and β positions. In most cases the predominant protein has the mobility of a γ globulin. In myeloma either other proteins are absent or, if present, are found in much smaller concentration. When an abnormal protein is found in both serum and urine the mobility is not necessarily identical.

(8) *The pattern in malignant disease.*—In nearly all the cases we have examined the α globulins are notably increased and often the albumin is diminished. In a minority the γ globulin is increased and this may be correlated with involvement of the liver. Examples of patterns we have obtained are shown in Fig. L, 1–3. In these cases the disease was fairly advanced and it may well be that in the early stages the pattern is normal. In a few cases of lymphoma the γ globulin has been found to be diminished.

(9) *The pattern in miscellaneous conditions.*—In Fig. M, 1–3, are shown patterns from an assortment of conditions in which well-marked deviation from normal is present.

In Cushing's syndrome the interesting feature is the decrease of the γ globulin. This is of particular interest in view of the effect of cortisone treatment in lowering raised levels of γ globulin in such conditions as the collagen diseases. In addition to the low γ globulin there is marked increase of the α_2 globulin. In sarcoidosis the γ globulin is notably increased in clinically active cases and there may be some increase of the α_2 globulin. Where the disease is relatively quiescent the pattern may be normal or show only an increase of the α_2 globulin. In primary xanthomatosis there is a marked increase of the faster moving β globulins. This is of interest since it is known that the β_1 globulins transport most of the serum cholesterol. We have encountered similar patterns in other conditions associated with raised serum cholesterol; in the nephrotic syndrome, however, this finding is absent.

(10) *The pattern in rare protein disorders.*—In Fig. N, 1–3, are shown patterns obtained from cases showing very rare protein changes in the blood.

In agammaglobulinæmia there is complete absence of γ globulin. This serum came from a young child who was under the care of Dr. S. Yudkin at the Whittington Hospital and was diagnosed clinically as a possible case of agammaglobulinæmia on account of repeated pyogenic infections. Probably the condition is congenital but this remains to be proved. In the case of macroglobulinæmia illustrated there is a very dense narrow band in the γ globulin indistinguishable from a myeloma band. This serum came from a proved case of macroglobulinæmia under the care of Prof. J. Waldenstrom in Sweden and 50% of the protein has been shown by Pedersen to be of high molecular weight in the ultracentrifuge. In cryoglobulinæmia the isolated cryoglobulin from a case of myeloma is shown to migrate as a γ globulin.

Summary and Conclusions

The usual significance of the changes in the electrophoretic globulin fractions may be briefly summarized by stating that:

(*a*) The α globulins are increased in high fever; tissue destruction; nephrotic syndrome (α_2 only).

(*b*) The β globulin is increased in conditions associated with increase of the serum phospholipids and cholesterol; myeloma (some cases).

(*c*) The γ globulin is increased in chronic infections; liver disease; collagen diseases; myeloma (some cases).

In certain conditions the electrophoretic pattern is virtually diagnostic, but in most cases it will show only non-specific changes. The extent of these changes will reflect the severity if not the nature of the underlying cause. Our experience suggests that paper electrophoresis yields results similar to those obtained by the elaborate classical method, and that it has a definite value in the routine investigation of certain conditions, such as obscure anæmias. With increasing application of the method of paper electrophoresis one may safely predict that other specific findings will be found which will increase its usefulness to the clinician still further.

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Dr. J. Hardwicke (Department of Experimental Pathology, University of Birmingham):

Serum and Urinary Protein Changes in the Nephrotic Syndrome

We define the nephrotic syndrome as that manifested by any patient with persistent proteinuria associated with hypoproteinæmia, œdema, a raised serum cholesterol and the characteristic plasma changes described later.

For investigation the problem has been separated into two broad divisions: (i) The renal lesion and the ætiology of the proteinuria, (ii) The relationship of the proteinuria to the plasma changes and to the symptomatology of the condition. This paper is concerned with some of the findings under the second head.

The serum and urine protein changes in the nephrotic syndrome are characteristic. Fig. 1 shows a normal serum, separated by paper electrophoresis (Hardwicke, 1954) and Fig. 2 a serum and urine

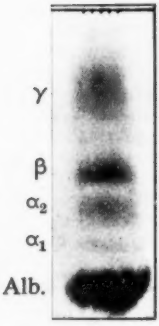

FIG. 1.—Normal serum proteins.

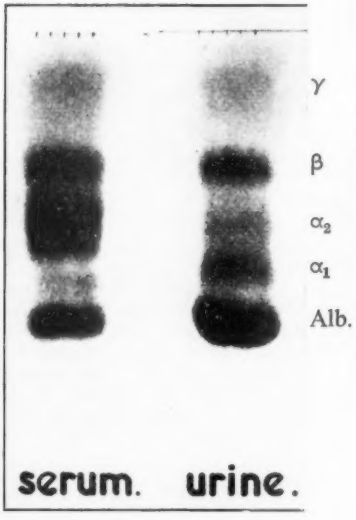

FIG. 2.—Serum and urinary proteins in the nephrotic syndrome. The serum is diluted 1/4, the urine undiluted.

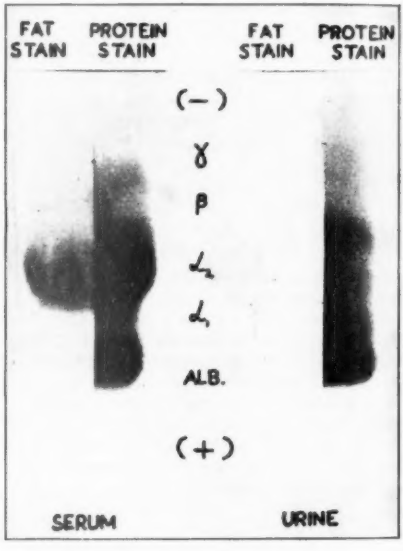

FIG. 3.—Serum and urinary proteins stained for lipid. The serum is undiluted, the urine is concentrated. × 2.

from a case of the nephrotic syndrome. In the serum the most striking changes are the low albumin and the high α_2 globulin levels. The urine shows variable proportions of albumin and the various globulin fractions in different patients, but the low molecular weight fractions (albumin, α_1 globulin and a β globulin) predominate while the high molecular weight α_2 globulin is virtually absent, in spite of the very high serum concentration. The serum lipid is also markedly raised, in association with the high serum cholesterol. This is shown in Fig. 3, in which one-half of the strip is stained with Sudan Black (Swahn, 1953). This increased lipid is associated with the slow β lipoprotein, while the fast α lipoprotein which migrates just behind the albumin, is lower than normal. The urine is strikingly free from lipid only a trace being seen in the α component. Technically this high serum lipid makes the paper method preferable to the classical U-tube electrophoretic analysis (Longsworth, *et al.*, 1939) in this type of case, since (in the U-tube) the lipid contributes to the analysis resulting in artificially low values for non-lipid containing fractions.

Fig. 4 summarizes the plasma changes, relating them all to the most striking alteration, the fall in serum albumin. It is apparent that the lower molecular weight α_1 and γ globulin fractions, which are lost in the urine, show a fall, while the high molecular weight fibrinogen and α_2 globulins are markedly raised; the combined level of β globulins which are a mixture of proteins, does not change significantly; it has, however, been shown that the β fraction lost in the urine is the low molecular weight iron-carrying globulin (Neale, 1954). These alterations in the globulin fractions only become marked when the albumin falls below 50% of normal. The changes are specific and do not appear in other forms of hypoproteinæmia such as occur with liver cirrhosis, idiopathic steatorrhœa, Whipple's disease, famine œdema or with the nutritional protein deficiency of kwashiorkor (Thompson, 1954).

Examination of the relationship between the total protein lost in the urine (gram/kg. body-weight/day) and the reduced serum albumin concentration in individual cases shows a high degree of correlation (Fig. 5), and the three cases shown conform to the same pattern. Case VII was suffering

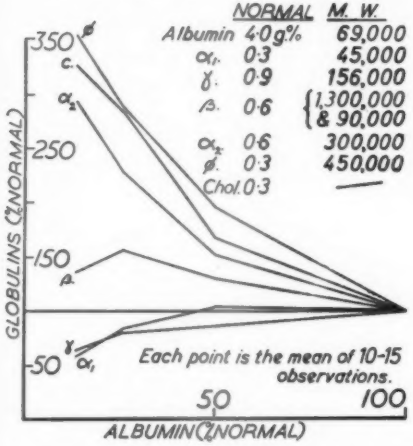

FIG. 4.—The alterations in concentration of the globulin components of plasma as the albumin level falls.

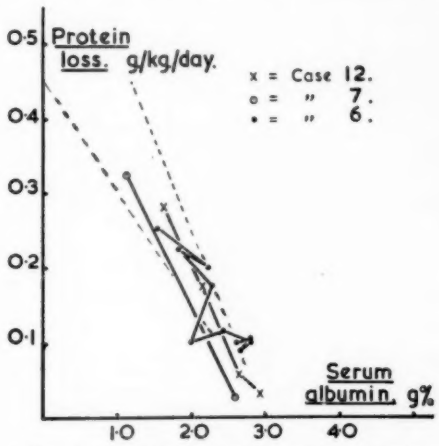

FIG. 5.—Relationship between serum albumin and daily urinary protein loss in individual cases.

from subacute nephritis in the nephrotic stage when first examined; he later progressed to chronic nephritis with isosthenuria, and as the proteinuria lessened so the serum albumin rose. Case XII was affected by constrictive pericarditis with severe proteinuria; following pericardial stripping the proteinuria diminished and finally disappeared, while the serum albumin rose steadily to normal. Case VI was a girl aged 13 with subacute nephritis who was recovering when observations were started; as the proteinuria fell the serum albumin again rose. It thus appears that in these cases, on adequate protein diet and under supervision, there is a maximum level of serum albumin compatible with a given daily protein loss.

All the cases examined, however, do not conform so satisfactorily. Fig. 6 shows the complete data, and a number of analyses show serum albumin levels disproportionately low for the protein loss; we believe that the most likely explanation is that the synthesis of protein is defective in these cases, either:

(1) Due to whole protein deprivation in the diet, or

(2) Due to specific metabolite deficiencies or metabolic disorder.

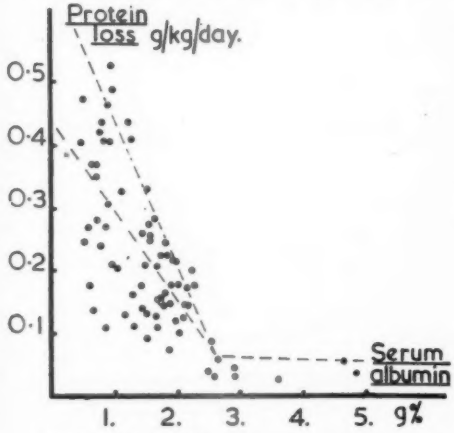

FIG. 6.—Relationship between serum albumin and daily urinary protein loss.

In favour of (1) is the observation that high protein feeding alone will, in many cases, raise the serum albumin level to the highest value usually seen in association with the daily protein loss. As the serum albumin rises, however, an increase in proteinuria must also occur; this is the result of the renal lesion already present (Squire, 1953), and does not indicate further damage; we do not therefore believe it is detrimental to the patient. The rise in serum level may be sufficient to induce a diuresis and to relieve the most distressing symptoms of the nephrotic syndrome.

In this series the nephrotic syndrome has appeared when the serum albumin was 1·0–2·0 grams % (25–50% of normal) this level being found with a protein loss of 0·15–0·3 gram/kg./day or 10–20 grams/day in a man of 70 kilo. While we believe that defects in protein synthesis may aggravate the fall in serum albumin associated with the proteinuria, more sensitive techniques, such as

the use of radioactive isotopes (Spector, 1954) will be required to supply the final answers, both as to the maximum protein synthesis possible on adequate diets, and as to the possible presence of specific deficiencies or disorders.

In conclusion, the nephrotic syndrome apparently arises in any case of proteinuria of sufficient severity (more than 0·2 gram/kg./day) and we have seen it occur: (i) In the course of progressive subacute nephritis with hypertension and microscopic hæmaturia. (ii) In a group of cases associated either with congestive cardiac failure, renal vein thrombosis or constrictive pericarditis. (iii) In a number of patients in whom no renal or systemic abnormality other than proteinuria and the characteristic plasma changes could be demonstrated; these we have called *uncomplicated nephrotic syndrome*.

The greater part of this work was carried out while in receipt of a grant from the Medical Research Council.

The work in this paper forms part of a programme of investigation into proteinuria, and Professor J. R. Squire and Dr. J. D. Blainey have given much encouragement and discussed the significance of results. I am indebted to the physicians of the Queen Elizabeth Hospital, Birmingham, and other local hospitals for the opportunity of studying many patients.

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Professor A. C. Frazer (Department of Pharmacology, University of Birmingham):

Blood Lipoproteins

This paper briefly reviews our present knowledge of the lipoproteins of human blood.

The importance of lipoprotein association in blood was first emphasized by Macheboeuf (1929), who prepared a lipoprotein complex with well-defined characteristics from horse serum. Since then a number of lipoprotein particles have been isolated by different methods. Pedersen (1945) described a lipoprotein isolated from human plasma. Gurd *et al.* (1949) isolated an α and β lipoprotein from human plasma by differential alcohol precipitation. Gofman and his colleagues (1950) separated a series of fractions with differing flotation rates by ultracentrifugation. The most interesting groups, biologically, appear to be the lipoproteins with flotation rates Sf 10/20 and Sf 30/100. The density relationships are shown in Table I.

TABLE I

Flotation rate	Density grams/c.c.
Sf 2	1·050
Sf 4	1·040
Sf 8	1·029
Sf 10	1·023
Sf 17	0·99

Sf 40,000 represents chylomicrons

The Properties of Blood Lipoproteins

The lipids and proteins are linked by various bonds to form a mixed lipoprotein molecule which, in spite of a high lipid content, displays the general characteristics of a protein. Other types of lipoprotein association may occur which give lipid characteristics to the complex; these have been termed proteolipids by Folch and Lees (1951).

The size of the lipoproteins varies. Gurd *et al.* (1949) concluded that their α lipoprotein was 300 Å long and 50 Å wide and had a molecular weight of 200,000. This corresponds in size to the smallest measurable chylomicron observed under dark-ground by Elkes *et al.* (1939). The β lipoprotein, on the other hand, was spherical, with a diameter of 185 Å and had a molecular weight of 1,300,000. It resembles the X-protein of Pedersen. The lipoproteins isolated by ultracentrifuge vary in size—the Sf 10/20 group have a mean diameter of about 250 Å.

The composition of the lipoproteins has also been studied: The α lipoprotein accounts for 3% of the plasma protein, contains 35% of lipid and 65% of protein. The β lipoprotein represents 5% of the total plasma protein and 75% of the lipid in fasting plasma. It contains 75% of lipid (2/5 phospholipid and 3/5 cholesterol) and 25% of protein. The lipoproteins isolated by ultracentrifugation at flotation rate Sf 4 contain 25% of protein, 30% of cholesterol, 45% of phospholipids and no glycerides. Glycerides begin to occur in the lipoprotein fraction of lighter density than the Sf 17 series and increase progressively, while protein, cholesterol and phospholipids decrease.

Variations in lipoproteins.—The most interesting information at present available on the variations in blood lipoprotein under differing physiological or pathological conditions is concerned with the amounts of Sf 10/20 and Sf 30/100 lipoprotein found on ultracentrifugation.

Effect of age and sex.—The blood of children contains low levels of the Sf 10/20 and Sf 30/100 groups. These groups tend to increase with age; below 40 this is more marked in the male, but after 40 there is no sex differentiation (Gofman *et al.*, 1951).

Diurnal variation.—No significant diurnal variations were observed in the Sf 10/20 lipoproteins; a small but definite diurnal variation was found in the Sf 30/100 group, related to dietary intake of fat (Chandler *et al.*, 1953).

Effect of hormones.—Sex hormones appear to alter the distribution of lipoproteins; changes are observed during pregnancy. Heparin and allied substances have a marked effect, causing an immediate decrease in the level of the Sf 30/100 particles and a delayed and less-marked decrease of the Sf 10/20 group (Chandler *et al.*, 1953; Graham *et al.*, 1951).

Choline and other lipotropic substances were thought to be ineffective in relation to the lipid deposits of atheroma, but a recent publication by Best and his colleagues (Wilgram *et al.*, 1954) suggests that this may not be the case.

Correlation with obesity.—Some correlation has been shown between the occurrence of obesity and the level of Sf 10/20 and Sf 30/100 particles (Gofman and Jones, 1952).

Correlation with atherogenesis.—There would appear to be a significant correlation between an increase in the levels of Sf 10/20 and Sf 30/100 lipoprotein particles and atherogenesis, both in experimental animals and human subjects. Improvement is claimed in patients with severe atheroma and concomitant pathological changes during periods when the levels of these lipoproteins are depressed by heparin (Graham *et al.*, 1951).

Correlation with blood lipid levels.—It has long been thought that blood cholesterol levels or the cholesterol/phospholipid ratio correlate significantly with atherogenesis. There is some indication that these blood lipid levels may be correlated with certain lipoprotein changes, but the evidence is conflicting. It has been claimed that the abnormal lipoprotein levels are no more highly correlated with atherogenesis than total blood cholesterol (Keys, 1952). The lipoprotein fractions regarded as of possible significance in atherogenesis account for about 10% of the blood cholesterol.

Functions of blood lipoproteins.—Lipoproteins and their constituent lipids—cholesterol and phospholipids—have been thought to play some part in lipid transport. Recent studies suggest that these lipids do not represent transportable lipid which is being moved from one place to another for the purposes of metabolism. The rate of utilization of these materials by the extra-hepatic tissues is slow and the main site of both production and utilization appears to be the liver (Entenman *et al.*, 1946). The levels in the blood, therefore, mainly reflect the situation in the liver. The smaller lipoproteins, including the Sf 10/20 group, may be structural components of plasma. The Sf 30/100 group contains the main transportable lipid, triglyceride esters—this group consequently shows diurnal variations.

The occurrence of lipid deposition in the blood vessels has been regarded by some as a sort of "super-saturation" of the blood plasma with lipid. The appearance of abnormal levels of Sf 10/20 lipoproteins was not incompatible with this view. Recent work, however, indicates a different trend of thought. The turnover of lipids in the vessel wall is different in the atheromatous as compared with the normal vessel. The question, therefore, arises whether the changes observed in the blood lipoproteins may be part of a wider abnormality of lipid metabolism affecting the blood vessel walls and perhaps other tissues (Biggs and Colman, 1953).

It would be unwise to attempt to draw any conclusions at present with regard to the precise significance of changes in the blood lipoprotein pattern. It may be accepted, however, that changes in the blood lipoproteins can be significantly correlated with atherogenesis and that these changes are reversible. If it is true that the blood changes are only indicative of a more generalized abnormality of lipid metabolism, it is not impossible that certain tissue changes may also prove to be reversible.

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Professor N. H. Martin (St. George's Hospital Medical School, London):

Experience with the Transfusion of Human Albumin into Patients with Established Liver Damage

Since 1950, when Kekwick and Mackay (1954) first produced pure human albumin by their ether fractionation method in quantities sufficient to make limited clinical trial possible, we have, in the course of a more general study, transfused and followed in the succeeding years 17 patients suffering from progressive liver failure. In this note two points only, out of the mass of accumulated data, are discussed. A general discussion of the complications experienced with the albumin has already been published (Martin, 1954).

Eckhardt *et al.* (1948) have shown that albumin whether hydrolysed or whole, given orally, was accompanied by a prompt increase in the daily output of urinary nitrogen.

In contradistinction, intravenous administration of human albumin into normal persons did not result in an immediate corresponding increase in urinary nitrogen excretion, there being a lag of about three days (Eckhardt and Davidson, 1950).

In Fig. 1 the results of balance studies on 3 patients with chronic liver damage which we have studied, illustrate the same pattern of lag as that observed in normal subjects. The patients were all at rest in bed through the whole period of observation, and had been on the protein intakes noted in the figure for at least three weeks before the metabolic studies illustrated. None of the 3 patients

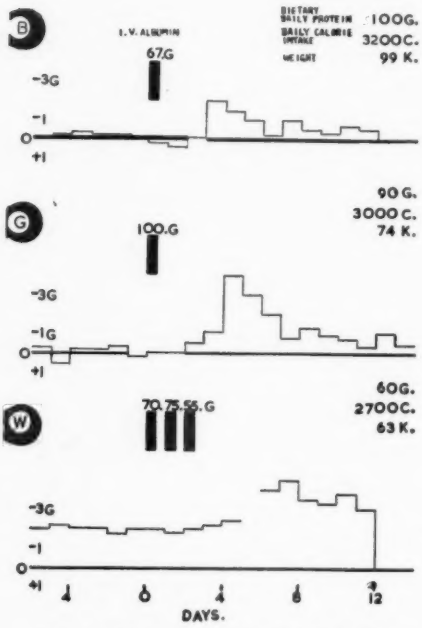

FIG. 1.—Nitrogen balance studies on three patients, B, G, and W, suffering from chronic progressive liver damage. The black transverse line at O indicates the point at which *oral* nitrogen intake was balanced by fæcal and urinary nitrogen output. The black oblongs represent the albumin transfusions each of which consisted of a 17·5% solution of salt-poor human albumin in 5% aqueous glucose solution (for sodium content ref. *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 286). The supplementary nitrogen introduced into the daily diet through the transfusion is not included in the total of the balance data. On day O each patient would be in markedly +ve nitrogen balance.

FIG. 2.—Qualitative chromatogram run in Butanol acetic acid on Whatman No. 1 filter paper. 50 μl. samples of each urine were mounted at the respective starting points. N = 8 a.m. specimen normal control. B = 8 a.m. specimen from patient R. S. prior to a transfusion of 75 grams of human albumin in five hours. A = 8 a.m. specimen from patient R. S. the morning after the transfusion was completed.

developed proteinuria during the period of study, though we have observed proteinuria in other patients receiving albumin intravenously in single doses of 100 grams and upwards.

Dent in 1947 had described briefly the increase and alteration in urinary amino-acid pattern occurring occasionally in patients with advanced liver damage. This does not occur regularly in all such patients. Nevertheless, as opportunity arose, we examined the effects of intravenous albumin on this phenomenon, especially in the "lag" period following transfusion.

Fig. 2 shows the immediate effect of intravenous albumin on the output of amino acids of a patient whose urine contained the marked increase described by Dent. As will be seen, there was an immediate and almost complete removal of amino acids from the urine which could not be explained on the grounds of a sudden excessive diuresis.

We had noticed in 3 patients suffering from extremely advanced liver damage a transient though striking improvement following single massive transfusions, and this observation was therefore of peculiar interest, hinting at the possibility that some of the free circulating amino acids may contribute to the clinical picture of hepatic coma, and that their "temporary immobilization" by albumin results in transient clinical improvement.

Walshe (1953) has made an extended study of the pattern of amino-acid excretion in liver disease and contends that the increased excretion is due to a raised level of free circulating amino acids rather than altered renal tubular reabsorption. A number of workers (Klotz, 1949; Martin, 1949) have demonstrated the extent to which albumin may interact with a variety of small molecules *in vitro*. We suggest that the alteration in urinary amino acids illustrated is due to a temporary "mopping up" of the excess of free circulating amino acids by the fresh transfused albumin. This "mopping up" would effectively, though temporarily, prevent their loss through the kidney in the urine.

This "mopping up" of amino acids is, in our experience, transient, the urinary amino acids returning to their pretransfusion level in the course of the next eight days.

Eckhardt and Davidson (1950) calculated that of 450 grams of human albumin given discontinuously to a normal human volunteer over a period of six days, 40·7% could be accounted for by the increase in total circulating albumin. This was in line with the earlier observation of Janeway and his associates (1944).

During the twenty-one days from the start of the albumin transfusions, 56% of the albumin transfused could be accounted for in the urine. Of this loss 43% was excreted in the fifteen days immediately after cessation of the transfusion and only 12–13% in the six days of the actual transfusion. It follows, therefore, that

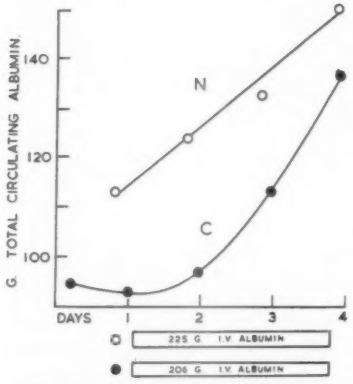

FIG. 3.—Alteration in circulating albumin levels over a three-day period. Grams total circulating albumin calculated from plasma volume and serum protein studies. N = normal volunteer. C = Patient with advanced progressive liver damage. Crown copyright: reproduced by permission of H.M. Stationery Office.

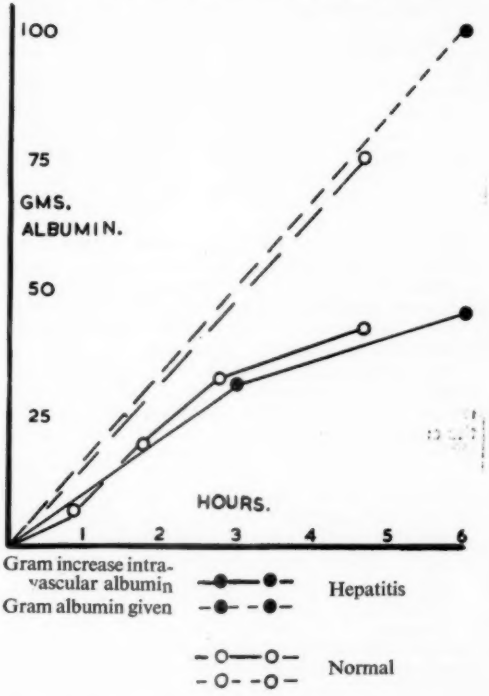

FIG. 4.—Albumin retained in the vascular compartment during the progress of a single transfusion of albumin maintained at a steady rate. Albumin concentration in transfusing fluid. 17·5 grams per 100 ml. 5% glucose in water.

Mr. H. D. Fairman: I propose to confine my remarks to my personal experience of the operative treatment of frontal sinusitis. The aim of treatment in the first place is to destroy the infecting organism by the exhibition of the appropriate antibiotic, and to promote drainage by the natural outlet in the middle meatus of the nose. Surgical procedures designed to attain the latter aim are inward fracture or amputation of all or part of the middle turbinal, resection of the nasal septum when there is a high deflection causing crowding in the middle meatus, and operations for the eradication of infection in adjacent sinuses, particularly the ethmoids and maxillary antrum. Lastly I would mention catherization of the sinus through the natural ostium with lavage, and the instillation of an appropriate antibiotic; I have employed this as an isolated procedure on several occasions, and also, as a variation of this basic technique, I have passed a fine polythene tube through a frontal sinus catheter, and have subsequently withdrawn the catheter, leaving the polythene tubing within the frontal sinus. Through this tube lavage has been done three or more times daily. Where these measures have not been effective in promoting resolution, or where the disease appears so acute or severe as to brook no delay, then an external approach to the frontal sinus will be necessary.

External operations upon the frontal sinus fall into three main categories:

(1) Simple drainage operations.
(2) Operations designed to enlarge the natural ostium with preservation of all or the greater part of the mucous membrane.
(3) Operations designed for the obliteration of the frontal sinus, with removal of the mucous membrane.

The literature records the failures of all these types of operation. Simple drainage is often insufficient. The operations designed to enlarge the natural ostium suffer from the defect that the diseased mucous membrane is left behind, the new opening tends to contract and therefore relapses are not uncommon. The operations for obliteration caused gross deformity and were not without recurrence owing to failure to remove some portion of the mucous membrane, and were also not without danger of causing an osteomyelitis. Nevertheless an operation for removal of the diseased mucous membrane, and obliteration of the frontal sinus has always appealed to me as being a logical procedure, and the use of the sulphonamides and the antibiotic agents has removed almost all the risks of spreading infection. Finally, when I heard Mr. R. R. Woods of Dublin, at the International Congress in 1949, describe an obliterative operation for frontal sinusitis without causing deformity, I was convinced that he had introduced a great advance in frontal sinus surgery.

In my experience external operations on the frontal sinus have been uncommon. At one of the hospitals at which I work, of 251 patients who were operated upon for the relief of sinusitis, 7 only had an external operation upon the frontal sinus.

The acute cases, requiring operation, of which I have had only 2, have been dealt with by a simple drainage operation, access being through the floor of the sinus through a small incision above the inner canthus of the eye, with the passage of a small bore Portex tube into the frontal sinus, the tube being then stitched to the skin. One case resolved. The X-ray appearances returned to normal and the patient became symptom free. The other case, complicated by the presence of a sub-periosteal abscess, was treated as above, and the abscess drained through a separate wide incision over the apex of the swelling. Nevertheless active infection still persisted. The incision over the abscess was subsequently enlarged, an area of osteomyelitis was removed, and entry to the frontal sinus attained. A sequestrum of the posterior wall was removed, and the sinus then dealt with as described by Mr. Woods. This patient is now quite well and has had no relapse to date.

In the chronic cases I have performed Woods' obliterative operation. There are 6 cases (8 frontal sinuses) in this series, and there have been no relapses so far. I have interpreted the operation as follows:

An incision is made below the hair-line of the eyebrow, beginning at the most lateral extension of the frontal sinus, and passing medially, and curving downward over the lateral aspect of the bridge of the nose to end half a centimetre anterior to the inner canthus. The supra-orbital vessels and nerve are divided if they get in the way. The soft tissues are lifted off the bone by subperiosteal dissection. The frontal sinus is entered through the floor, using a gouge. With suitable punch forceps, the entire floor of the sinus is removed. The mucous membrane lining is then dissected from the sinus, using a variety of blunt dissectors. Then a piece of gauze is pulled through the infundibulum into the nose, and the mucous membrane removed by abrasion. Lastly the cavity is filled with penicillin sulphathiazole powder and the wound close-stitched in layers. A pressure bandage is applied and the patient instructed to refrain from nose blowing. The operation is performed under penicillin-sulphonamide cover, and this cover is provided for at least three weeks post-operatively.

I have encountered no serious complications. Two patients developed considerable swelling in the region of the incision which I attributed to inadequate bandaging, and one of these required aspiration of a quantity of blood-stained serum. Both patients made a satisfactory recovery without disability.

All patients have experienced some degree of diplopia. In most the disability has been slight and of a temporary nature and has not been the cause of spontaneous complaint. In one case the diplopia has persisted and has not responded to treatment by an ophthalmic surgeon. Even so the disability is very slight.

Adequate antibiotic treatment both of the acute case and of the post-operative state is of paramount importance. I doubt whether the procedures which I have described would have proved so trouble free without their use.

In all I have treated 11 frontal sinuses in 9 patients by this technique; 8 frontal sinuses in 6 patients because of chronic disease; 1 frontal sinus because of acute disease; 2 frontal sinuses in 2 patients from whom I had removed an osteoma. So far, there has been no relapse and no serious complications.

Mr. R. G. Macbeth: *The Osteoplastic Operation for Chronic Infection of the Frontal Sinus.*—The treatment of chronic frontal sinusitis had remained one of the most unsatisfactory items in rhinology. This was illustrated by the variety of operations described for the relief of the condition, the reluctance shown by most surgeons to operate upon the frontal sinus at all, and the number of cases which came for revision.

The operations had fallen broadly into two groups: (*a*) Those designed to enhance drainage into the nose while preserving natural contours. (*b*) Those designed to eradicate an irreversibly diseased mucosa, while disregarding disfigurement.

Summary

Dissatisfaction with the accepted methods was noted. Methods aiming at enlargement of the fronto-nasal duct and consequent drainage into the nose were unphysiological; obliterative operations, though surgically sound, were disfiguring.

Appreciation was expressed of the osteoplastic operation of Gibson and Walker (1951 and 1954), and experience with 16 cases over a period of two years was mentioned. In all cases up to date the patients had been relieved of their complaints. The method essentially consisted in turning the anterior wall of the sinuses forward attached to the forehead skin as an osteoplastic flap. The blood supply to the bone was thus preserved and an excellent exposure obtained.

Modifications of technique were described, also a method for "mapping" the outline of the sinuses on the forehead devised by Dr. P. W. E. Sheldon, as follows:

Skin marking the frontal sinuses (Dr. P. W. E. Sheldon).—During the first year that the frontal osteoplastic flap operation was in use at the Radcliffe Infirmary, the frontal sinuses were marked by sticking about 8 or 10 small pieces of wire on to the forehead with adhesive plaster. A series of radiographs were taken and the wires moved until they coincided with the margins of the frontal sinuses. When the wires were in correct positions, a line was drawn to link them up, and they were then removed. This method was cumbersome and time wasting because the X-ray examination had to be repeated three or four times.

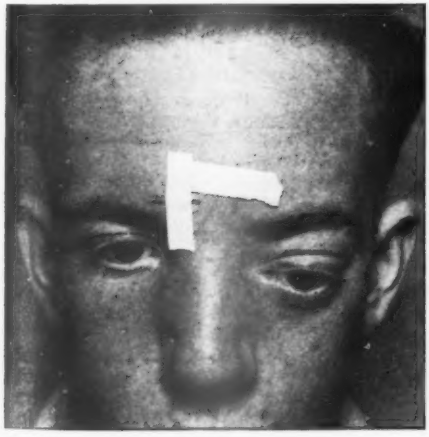

FIG. 1.

FIG. 2.

Their latest method was to stick two pieces of wire at right angles on the forehead, one on either side of the mid-line, about 1 in. apart, and 1 in. above the nasion (Fig. 1). Two radiographs of the frontal sinuses were taken, and one of these was dried rapidly. The film outside the margin of the frontal sinus was cut away, and then the remainder of the film was placed on the patient's forehead, so that the images of the two wires coincided with the original pieces of wire. The asymmetry of these wires immediately indicated which way round the film should be placed on the face (Fig. 2).

An indelible pencil traced round the margin of the film showed the outer limits of the frontal sinuses. The wires were now removed. Since the object film distance was small, there was virtually no enlargement or distortion of the image. A more accurate representation might be obtained by tracing the outline with a fine pen-nib.

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Mr. C. Gill-Carey said that the evaluation of different methods of treatment was aided by the study of large numbers of case reports covering a number of years.

On examining the results of 408 cases operated on by the external route (276 from the Massachusetts Eye and Ear Infirmary, covering a fifteen-year period up to 1944, and 132 from the Royal National Throat Hospital, a six-year period up to January 1954) two main facts emerged: chemotherapy had almost completely removed the fear of death, but no such dramatic improvement could be seen in the results of surgical treatment.

Approximately half the American cases were treated without the aid of chemotherapy. In the whole series the percentage of mortality was 15; but there was only one death in the latter part of the series when chemotherapy was used. In the 132 cases from the Royal National Throat Hospital there was one death. If the necessity for a second operation by the external route were classed as a failure, the proportion of failures were: Massachusetts Eye and Ear Infirmary, 34 per cent, and the Royal National Throat Hospital 29 per cent.

MASSACHUSETTS EYE AND EAR INFIRMARY
Period fifteen years to 1944
(Approximately half before Chemotherapy and Antibiotics)

	Patients	Operations	Average operations per patient	Mortality
Total	276	447	1·6	15%
Failures	95	266	2·8	—
Percentage failures ..	34·4%	—	—	—

ROYAL NATIONAL EAR, NOSE AND THROAT HOSPITAL
Period six years to January 1954

	Patients	Operations	Average operations per patient	Mortality
Total	132	199	1·5	0·7%
Failures	39	106	2·7	—
Percentage failures ..	29·5%	—	—	—

Analysis of the causes of failure showed close correspondence with Weille's conclusions. Neither the operations designed to improve drainage, nor the obliterative operations, were free from a considerable failure rate. In the first type of operation most failures were due to stenosis of the nasal opening, and in the second to incomplete removal of mucosa.

In the speaker's view, none of the operative techniques now described differed materially from those used in the past. He held the view that the prognosis was influenced by the type of sinusitis; pure infective sinusitis usually presented no difficulties, but in hyperplastic, polypoid disease, which was a local manifestation of a general disease, the prognosis was uncertain.

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Mr. R. R. Woods said that he would confine his remarks to the operative side of chronic frontal sinusitis: he thought a distinction must be made between the approach that one used in order to get at the frontal sinus and the method whereby one dealt with the sinus when exposed. It might be approached from the orbital route as he had always done and as Fairman did or by the osteoplastic method as Macbeth and Gibson and Walker had described. The orbital approach was undoubtedly the lesser operation. He made the incision entirely in the eyebrow and he did not think that the incision should go outside the hair-bearing area of the eyebrow. Further the removal of bone from the floor of the sinus left a kind of safety valve by which one could always tell if infection were present. If there were no œdema of the eyelid everything must be all right.

When one turned to the method of dealing with the sinus itself, he thought that the methods which Mr. Fairman and Mr. Macbeth had been using were both basically the same, and depended on the principles which he had advocated before the Section in 1951. These principles were (1) closure of

the frontal duct and (2) removal of all mucous membrane from the sinus, leading to its obliteration by fibrous tissue or bone. Reinfection could not occur if the frontal duct was closed and the sinus as such had ceased to exist.

He showed X-ray films of a case that had been operated on in 1940. These showed that the sinus had been obliterated by bone.

He showed X-ray slides of a woman who had a chronic infected right frontal sinus, and an infected right ethmoid. The frontal sinus was operated on, but the ethmoid was not touched. Nine months after operation the frontal sinus was obliterated, but the ethmoid cells had recovered and were completely clear. The ethmoid was not the key to the frontal sinus. This was only an excuse for failed operations. The key to the frontal sinus was a properly planned and properly performed operation on the frontal sinus.

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Mr. V. E. Negus, who was invited to speak, said that he had come rather to listen, because he had already expressed his views on the treatment of frontal sinusitis in StClair Thomson's book "Diseases of the Nose and Throat" (1948, 5th edit., London) and the method described there for the treatment of chronic frontal sinusitis was the one that he had followed for the last twenty years or more. It was based on the original operation of Howarth, but without cutting the supra-orbital nerve, which often led to supra-orbital neuralgia. A plastic tube and skin graft were introduced, the latter as recommended by Seiffert, Nager and others. In his hands and in the hands of those associated with him at King's College Hospital it had been satisfactory. He did not believe it was necessary or desirable to remove the lining of the frontal sinus. If one left a tube in for ten days with a properly placed skin graft the ciliated epithelium still functioned on the walls of the frontal sinus, on the nasal septum and on the septum between the two sinuses, preventing stagnation of secretions; the method was not unphysiological. In about 3 cases in 100 the duct had become closed for some reason and a simple operation had been necessary to reopen it and put in a tube with a small skin graft. He had been under the impression that the osteoplastic flap had been abandoned; he thought it was making heavy weather of the approach, which was easy with a small and almost invisible incision.

Mr. Ellis, going over the subject very thoroughly and showing cases with a fluid level in the frontal sinus, had made no mention of the washing out of the antrum. Mr. G. H. Bateman, when Registrar at King's College Hospital, collected a number of the speaker's and other cases and noted the fluid levels. All of them had the antrum washed out, and all of them recovered thereby; there were no antibiotics in those days.

Professor G. Dohlman (Lund), said that in his experience there had been a great many cases operated on by enthusiasts with very good results, but always with a remaining narrow passage to the sinus. In many cases, however, it might be doubtful if simple drainage, and a careful conservative treatment of sufficient duration would not lead to even better results. The modern antibiotics gave much greater support in this work than any extended surgical procedures could do.

If only the mucosa were involved, the inflammatory changes, however bad-looking, would invariably return to almost normal function. But if there were inflammatory changes extending into the bone resulting in osteitis or osteomyelitis, then nothing was gained by removing the mucosa leaving the bone surface open to secondary infection. The treatment of the osteitis with antibiotics, and a long-standing conservative treatment, seem to be more efficient than any surgical interventions, except the simple openings for drainage.

Mr. J. C. Hogg said that he had been much interested in Professor Dohlman's views. Simple drainage of the sinuses by an opening through the inner margin of the eyebrow, with the introduction of an elastic rubber tube in the naso-frontal duct had in years gone by been very effective in relieving frontal sinusitis. On the whole he preferred, however, the classical operation described by Mr. Negus, as in the vast majority of cases this brought about a rapid relief of the symptoms. He had listened to Mr. Macbeth's paper with great interest, but could not agree that this procedure was justifiable, except in the most advanced and resistant cases.

Mr. W. O. Lodge considered that there was some danger of the discussion becoming controversial because they were talking about different types of cellular development calling for different modes of operation. He thought they were all in agreement with the more conservative treatment and with the sound views which Mr. Gill-Carey and Mr. Negus had put forward.

Mr. J. H. Otty said that he came out on the side of Mr. Woods. He had seen quite a number of failures. In obliterating operations all the mucous membrane was removed from the frontal sinus and then the ethmoid was lightly packed and the fronto-nasal duct closed. The orbital incision should

be kept open as in the simple mastoid operation. Occasionally the wound healed with a little depression. Having seen Mr. Woods' operation he followed out his technique but still removed all the ethmoidal cells as far as possible. He was sure that it was wrong to try to keep the fronto-nasal duct open.

Mr. S. W. G. Hargrove believed the primary source of infection in frontal sinusitis to be in the ethmoid. He believed that the fronto-nasal duct should not be disturbed and the ethmoidal cells should be removed in the fronto-ethmoidal region. He agreed with Professor Dohlman that there were two types of chronic frontal sinusitis, one in which the infection involved the mucous membrane only and the more extensive sinusitis in which an osteitis was present. Mr. Woods had described a method of obliterating the frontal sinus. He could not understand how the frontal sinus became obliterated by using Mr. Woods' method and he presumed that it was the sterile blood-clot method as used in a cortical mastoidectomy. He found that in many instances where he had had to reopen a cortical mastoid, the mastoid cavity had a filling defect where this method had been used. The bone was sclerosed and no obliteration had taken place. Could this not happen in this method of obliteration of the frontal sinus? He also could not see how one could obliterate the fronto-nasal duct without involving the agger nasi cells.

Mr. Maxwell Ellis, in reply, said that he thoroughly agreed with Mr. Negus that acute maxillary sinusitis often accompanied acute frontal sinusitis. In the case he had shown on the screen, the maxillary sinusitis also present was, of course, treated by all the usual methods, including antral lavage. One must clearly distinguish between acute and chronic infections, as they were two very different things. When the tissues are unhealthy and possibly necrotic, they must be excised and removed completely and the measure of failure was the measure of neglect to do so. When ethmoidal cells were involved, as they often were, they, too, must be removed. Cases of chronic frontal sinusitis were few. In the last four years he had had only six frontal sinuses which he thought should be operated on.

Mr. Hogg had spoken of the difficulty of preventing mucosal ulcer as a result of the pressure of the tube on the septum. This could be prevented by enlarging the pyriform aperture so that the tube could lie more vertically.

Finally, it was suggested that there were some tissues which should not be sacrificed even if irreversibly diseased. He did not know what they were, or how they were to be recognized.

Mr. H. D. Fairman said that he had opened the ethmoid on several occasions, particularly in one of the cases he had just shown. He had made a tremendous opening into the nose but there did not seem to be any untoward occurrence.

Section of Pædiatrics

President—C. T. Potter, M.D., F.R.C.P.

[*March* 26, 1954]

DISCUSSION ON THE SIGNIFICANCE OF CONVULSIONS IN INFANCY AND CHILDHOOD

Dr. J. P. M. Tizard: *Convulsive Threshold and Convulsive Diseases* [*Abridged*]

Most textbooks divide fits on an ætiological basis into the symptomatic, caused by fevers, brain tumours, brain injury, &c., and the idiopathic, which include infantile convulsions, pyknolepsy and true epilepsy. Is there justification for this type of division?

As regards symptomatic epilepsy, we do not really know the effective cause, in the Aristotelian sense, of any fit. It is clear that a high fever cannot in itself be the cause of a fit; were it so, any individual would convulse whenever his temperature reached a certain critical height, whereas we know that this only occurs in a minority of children. Moreover, even in such a child the fit takes place as the temperature rises to a certain level and fits do not continue if the fever remains at the same level. Similarly a cerebral tumour cannot itself be the cause of a fit, as, if it were, the patient would convulse continuously and not intermittently.

The commonly held view that epilepsy can be subdivided into separate conditions has been expressed satirically by Buchanan (1952): "There is a widespread belief that there is a subtle difference between convulsions occurring in infancy and those which appear for the first time in childhood or in adult life. There is an even more deeply rooted belief that those convulsions of infancy or childhood which are associated with a feverish illness have no serious connotation and that those which take place apparently spontaneously are evidence of a sinister disease called epilepsy."

It seems probable that in the production of a fit there is usually more than one causative factor involved and this brings us to the concept of convulsive threshold.

We may take the view that there is no fundamental difference between epileptics and non-epileptics. Any individual given an adequate stimulus will have a fit, but the nature and degree of the precipitating agent varies from person to person. At one end of the scale are those who will only convulse in response to a severe electric shock, or an injection of insulin or leptazol, while at the other end are those in whom fits occur spontaneously, that is to say the precipitating factors are not detectable. In between these extremes one would place those individuals who convulse in response to conditions such as high fever, brain injury and cerebral tumour, conditions which might not cause fits in others with a higher convulsive threshold.

There is evidence derived from family histories and electroencephalograms that a predisposition to fits may be inherited. Claims have been made for a high family incidence of fits in cases of febrile convulsions and convulsions associated with brain damage (e.g. Lennox, 1947, and Lennox, 1951). Rosenbaum and Maltby (1943) found a higher incidence of EEG abnormalities and family histories of fits in mothers who convulsed with toxæmia of pregnancy, than in those who had toxæmia without convulsions. Williams and Sweet (1944) found EEG dysrhythmia similar to those of idiopathic epilepsy in patients who had convulsions during inhalation anæsthesia. The view that we are all potential epileptics, but have varying degrees of natural resistance receives some support from these studies. It certainly provides a useful method of approach to the parents of a child who has fits in discussing the nature of convulsions and removing the sting attached to a diagnosis of epilepsy. But it is clearly a simplification of the truth and it is worth considering to what extent it is true at all.

As regards "symptomatic epilepsy" there are many authorities who maintain that there is no evidence of hereditary predisposition in that small minority of patients who develop fits following head injury. Quadfasel and Walker (1947) found a history of fits in 4·4% of families of patients suffering from post-traumatic epilepsy, compared with 3·4% in controls and 17% in families of idiopathic epileptics.

Similarly there seems to be no evidence of an inherited predisposition in patients with cerebral tumours who convulse. The type of tumour and its location seem to be the important factors (Ziskind and Ziskind, 1938).

In contrast, the incidence of fits in the families of children with febrile convulsions, far from being too low to suggest an heredity susceptibility, appear paradoxically to be too high! For, if one accepts

the view of a variable convulsive threshold, hereditarily determined, one would expect the family incidence of fits to be highest in so-called idiopathic epilepsy and lowest where the immediate precipitating factors were most obvious. However, the incidence of a family history of fits in children with febrile convulsions is said by Margaret Lennox to be no less than 45%, a figure far higher than any estimate for idiopathic epilepsy. It is also considerably higher than other estimates of the family incidence of fits in cases of febrile convulsions (e.g. Zellweger, 1948). But if we accept a high incidence and if, as suggested by Davidson (1953), the relatives also suffered from febrile convulsions, it would suggest that some of these patients do not have a lowered threshold for fits, so much as a peculiar reaction to high fever, vascular—as suggested by Zellweger—or biochemical; a reaction which would be sufficient to produce a fit in anyone.

It might be this reaction rather than a tendency to fits which is inherited. This would clearly not apply to all cases of febrile convulsions because one cannot deny that some patients continue to have fits in later childhood with less obvious precipitating causes.

In this connexion it should be mentioned that much of the literature on the family incidence of fits is unsatisfactory, both because of failure to define what constitutes, for the purpose of the study, a family or a history of fits, and because of a lack of genuine controls.

In discussing the threshold theory as applied to idiopathic epilepsy one must first mention the concept of Williams (1950), who suggests that there are two factors concerned in the production of fits—the tendency of the brain to produce abnormal electrical discharges and the natural resistance to these discharges provoking clinical fits. There is considerable support from electroencephalography for this hypothesis.

Secondly, the EEG has emphasized that the fit as a symptom differs qualitatively not merely quantitatively; for instance that *petit mal* is not simply a little *grand mal*. The bilaterally symmetrical thrice a second spike and wave has a particular significance in terms of the natural history of the disorder it accompanies. The presence of occipital delta rhythm in the EEG tracings of some patients with *petit mal* may also differentiate another form of minor epilepsy. Recently Hess and Neuhaus (1952) have described the particular EEG pattern which accompanies "Blitz, Nick-und Salaamkrämpfen" and Gibbs, Fleming and Gibbs (1954) have reported similar EEG findings in "infantile spasms" (probably the same condition).

These EEG studies and the clinical investigations they prompt suggest that there are different types of idiopathic epilepsy and that the theory of convulsive threshold must be limited in its application. Too great an emphasis on convulsive threshold in its hereditary aspects might slacken the search for the pathology of so-called idiopathic epilepsy, that is of disorders of at present unknown ætiology, of which fits are the main or the only symptom.

It is at least possible that we shall return to the view that "infantile convulsions", "pyknolepsy", "febrile convulsions", &c., are, after all, separate disease entities with similar symptoms.

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Dr. W. A. Cobb: *The Diagnostic Value of the EEG in Epileptic Children*

I intend to discuss only certain aspects of the EEG in epileptic children. It is not possible to work with the EEG in general neurological practice without seeing many examples of the 3 c/s spike and wave episode. While the purely electrical classification of fits by the Gibbs' and Lennox was an oversimplification, I think we should retain a part of it. If an epileptic attack occurs without the simultaneous occurrence of spike and wave complexes it is justifiable to regard that fit, whatever its nature, as of another kind from pure "*petit mal*", giving that term a more restricted meaning than "minor fit". On the other hand, episodes of repetitive spikes and waves in the EEG do not make it certain that the subject must suffer from such attacks.

For some time we have been collecting EEGs which have two features in common: the occurrence of 3 c/s spike and wave complexes during, and sometimes between, attacks, and the presence of an occipital delta rhythm (Fig. 1). This rhythm is usually at 3 c/s, often of high voltage and nearly

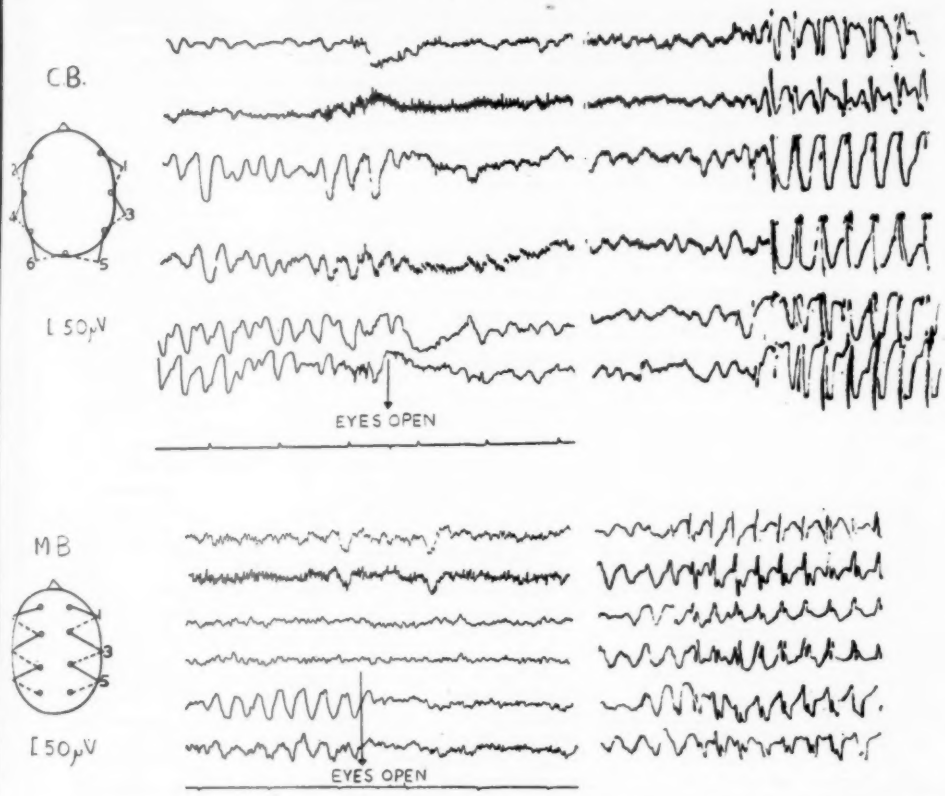

FIG. 1.—Records from epileptic siblings, C. B. aged 4 and M. B. aged 10, showing in each case a bilateral 3 c/s occipital rhythm which is blocked when the eyes are opened. The records on the right show the beginning of *petit mal* attacks in the two cases, associated with spike and wave complexes which have quite different distribution from the occipital delta rhythm.

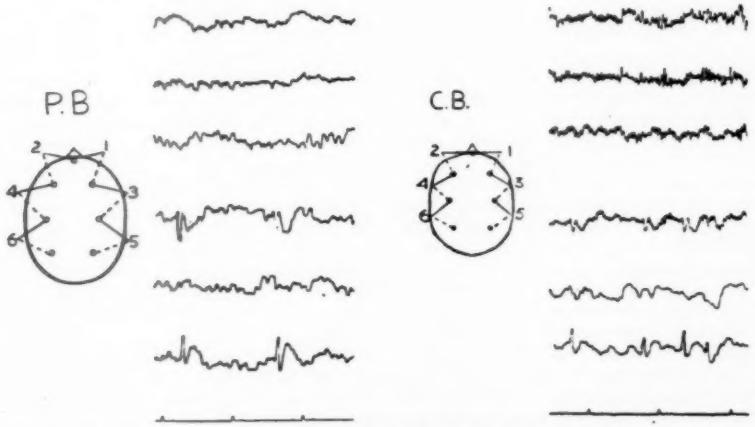

FIG. 2.—Focal spikes occurring in the EEG of an epileptic child (C. B., also shown in Fig. 1) and of his non-epileptic binovular twin, P. B.

continuous, and has bilateral foci in the occipito-temporal regions; it is strikingly blocked by eye opening and usually by startle, and increased in continuity and amplitude by overbreathing. Sometimes each wave (or many of them) is notched, suggesting the presence of a very small spike, but when the true spike and wave episode occurs its complexes are quite different and its distribution over the scalp much wider. The patients who show this combination of abnormalities are all young and it can be assumed to disappear at or about puberty; they all suffer from the typical absences of *petit mal*, and some also occasional major fits. We have little doubt that a family history is even commoner in them than in a general group of sufferers from *petit mal* at this age. While the epilepsy of these children is more than usually difficult to control by any of the usual drugs there is a fair amount of evidence to show that their fits cease spontaneously at puberty; it may take a number of years of careful follow-up to put this point beyond doubt but it seems likely that we have a means of recognizing a type of epilepsy which is hard to treat successfully but which has a good prognosis, something which perhaps corresponds with the definition given to the somewhat outmoded term of pyknolepsy. I should add that some years ago Walter described a rather similar group of cases which he thought fell within this definition; in these the spikes and waves differed from the usual in being mainly occipital and being blocked by eye-opening; while we see these cases occasionally they do not seem to correspond with the group which I have described, and this blocking response can certainly occur in adults.

Before leaving the subject of spike and wave a word on one particular aspect of therapy may not be amiss. Some years ago Lennox and Gibbs published a paper which gave rise to the impression that Tridione was a nearly specific treatment for this type of episode and many requests for examination still contain the query "? suitable for Tridione". As I have said it is probable that every true *petit mal* attack is accompanied by spikes and waves, and Tridione is certainly good treatment for *petit mal*, but spikes and waves may occur in association with mixed types of attack and even *grand mal* alone, for which Tridione is often very bad treatment indeed. The EEG may be used, therefore, to establish that the minor fit is true *petit mal* but beyond that the use of Tridione should be determined by clinical considerations alone.

After the 3 c/s spike and wave the most certain indication of epilepsy is the presence of spikes, or their longer variant, sharp waves. The focal spike may occur in constitutional epilepsy or as a fairly accurate topographical representation of local disease; clearly the distinction between these two causations is very important, but unfortunately it is often impossible. In idiopathic epilepsy a focal spike may occur in the absence of focal fits, or its site may coincide with the expected source of the focal attack, or it may not; rarely it may even occur in an unaffected sibling. (Fig. 2). The form of the spike may be identical in symptomatic and idiopathic epilepsy so that its presence is often a warning to reserve judgment and watch the patient for the development of localizing signs.

The presence of bilateral episodes, or of a general symmetrical abnormality, as well as the focal spike, favours idiopathic epilepsy, while a normal EEG remote from the spike focus, with slow waves in its immediate area is suggestive of a local lesion. It is always wise to repeat the EEG several times in such cases; if the spike disappears, perhaps to return later, it is of no diagnostic help, but if it goes from one area and reappears in another, or in both simultaneously, it becomes rather unlikely that there is a single causal lesion. On the other hand, we have numerous patients, mostly adults, whose spikes or sharp waves are always in the same place, but in whom pneumonencephalography, arteriography and the passage of time have entirely failed to demonstrate a lesion.

It is, in fact, rather unusual for a spike to stand out alone from the background and it is much more commonly followed by some sort of slow wave. Often these are variable and the spike is the constant dominant component, but equally commonly the association is so constant that one has to think of a complex rather than of a single spike. Again the form of this complex is little guide to the nature of the epilepsy, and it may be indistinguishable from the spike and wave of *petit mal* except in its focal distribution. Even this distinction breaks down at times for I have seen a purely unilateral spike and wave episode which would become bilaterally synchronous during overbreathing and then be accompanied by a typical absence.

Next I shall discuss certain aspects of symptomatic epilepsy as revealed by the EEG; I shall not consider tumours, where the indications are more often those of the encroaching lesion than of heightened cerebral irritability, and shall concern myself first with those atrophic lesions arising at birth or in early life, which, in their greater degrees, reveal themselves as infantile hemiplegia or diplegia. In the National Hospital we have had unique opportunity to study the effects of these gross lesions because of the series of nearly thirty hemispherectomies performed by Mr. Wylie McKissock. Certain aspects of the electrical responses to such lesions could hardly have been recognized without access to this pathological material and the post-operative records.

The degree of abnormality varies very greatly and does not seem to bear much relationship either to the extent of the damage or to the frequency and severity of the fits, though it shows some tendency to decrease with advancing age. There may be evidence of the presence of a cyst or of extensive gliosis in the form of an area of relative electrical silence, and around this it is usual to find slow-wave activity, often with focal spikes arising from one or more areas; these are findings to be expected with

any large atrophic lesion. It is the changes in the normal hemisphere which are disconcerting and instructive; here there may also be much slow activity, but also many random spikes or sharp waves, apparently unassociated with those on the damaged side; so far as we can tell there is no means of distinguishing these spikes from those due to bilateral lesions, although removal of the damaged hemisphere causes them to disappear and the clinical improvement of the patients argues against bilateral damage. At present we have to admit that the EEG is of little value in choosing patients for hemispherectomy because of this paradox.

Another type of disturbance which we have seen in a number of patients is the occurrence of episodes, either during waking or sleeping, of a kind which we associate with a deep mid-line origin, because of their rhythmicity or responsiveness to various stimuli, or their occurrence as arousal responses during sleep. They are usually bilaterally synchronous and their peculiarity in these hemiplegic patients is that they are unilateral or nearly so, and occur on the *normal side*. Our tentative explanation for this is that they are essentially bilaterally synchronous but cannot get through on the abnormal side because of the damage there; their presence raises doubts of the integrity of the thalamic or brain-stem nuclei but the post-operative results do not at present show convincing evidence that these cases do worse than others.

There are many young patients whose EEGs show spike and wave-like episodes, in which the complexes are slower and the spikes longer than in true *petit mal*; the slower and more atypical in form they are, the more certain is it that the case is one of symptomatic epilepsy. Sometimes these spike and wave variants are focal, but often they are bilaterally synchronous and the choice between idiopathic and symptomatic epilepsy may not be easy. The EEGs range from those in which there are distinct episodes of slow complexes to the other extreme in which there is a continuous background of slow waves, on which spikes, sharp waves and polyphasic waves are superimposed in a quite random manner (Fig. 3). We have found this latter condition only in young children with fits and

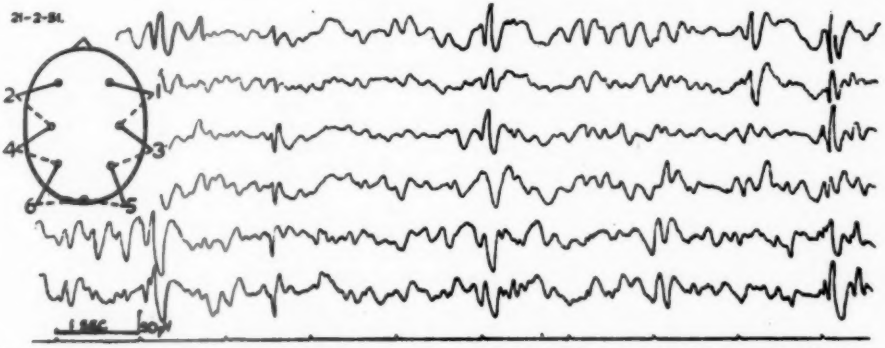

FIG. 3.—From the time of a minor head injury at nine months this child, aged 4, had jerking of the limbs and, later, major epileptic attacks, associated with progressive mental deterioration. Signs of involvement of the pyramidal and cerebellar systems were present and the optic fundi showed cherry-red maculæ. Diagnosis: Tay Sach's disease.

mental deterioration; in several of them one or other form of cerebral lipidosis has been proved and in a number of others this has been the preferred diagnosis, though without pathological confirmation. On the other hand, in the few confirmed cases of Schilder's disease which we have seen, despite the occurrence of fits, there have been no spikes or sharp waves.

Finally, there is the disease, uncommon, though less rare than was thought, of subacute progressive panencephalitis, to use Greenfield's general name for the two forms described by Dawson and van Bogaert. In these cases the EEG shows a complex of slow waves recurring at nearly regular intervals of 4–20 sec.; the complex is very variable from case to case but remarkably stereotyped in any given record (Fig. 4); it is this, and its regularity of recurrence, which give it unique diagnostic value. The jerks which are so characteristic of the disease occur at the same time as the complexes, but are not directly dependent on them as either may be present without the other. In fact, in some cases which we have followed over many weeks, the complexes have been present on some days but not on others, so that their absence from a single record does not exclude the diagnosis. In well over 20,000 records I have only twice seen anything resembling the periodicity of subacute encephalitis and in these cases the complexes were not highly stereotyped; over 30 cases have been published or are known to me and in all which have been examined more than once, the repetitive complexes have occurred. There is, however, one published case showing repetitive complexes apparently associated with an acute

encephalitis which recovered. I think that the specificity of this type of EEG is at least as high as that of the 3 c/s spike and wave for idiopathic epilepsy.

While the major contribution of electroencephalography to the study of epilepsy is perhaps a new

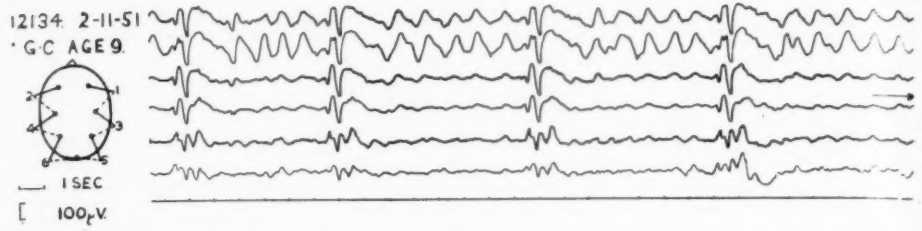

FIG. 4.—Showing the characteristic repetitive stereotyped changes associated with subacute progressive panencephalitis. This child had been ill for seven months, and died three months after the record was made.

point of view with a wider horizon, it has very real value in the diagnosis of the individual case, even though its vagaries and inconsistencies are still baffling and, particularly in children, its techniques and interpretation difficult.

Dr. L. Crome: *The Morbid Anatomy of Epilepsy in Mental Deficiency.*

Epilepsy is common among mentally defective children; 185 out of a total of 777 patients are classified as epileptics at the Fountain Hospital, an institution devoted chiefly to low-grade defectives up to the age of 15. I have examined the central nervous systems of 61 epileptics in a series of 118 consecutive autopsies. 24 of them were girls and 37 boys, their mental assessment being: imbeciles 9, and idiots 52. All the cases were under 15 years: 80% under 5; the mental assessment is therefore only approximate. The epileptic fits were described as major in 40, minor in 5 and mixed in 5 cases. They were atypical in 2 and not specified in a further 9 cases.

These figures convey, however, a false sense of precision. The clinical diagnosis of epilepsy in low-grade defectives may be extremely difficult and is often impossible. Fits range from questionable momentary lapses, dreaminess, screaming fits and more definite *petit mal* attacks through myoclonic jerks to definite *grand mal* and these may often co-exist in the same patient.

[Lantern slides illustrating some of the abnormalities were then shown].

The great variety of structural nervous defects in these patients explains why the search for specific epileptogenic lesions was unsuccessful and has now been abandoned.

All the brains examined in this series showed structural change, frequently multiple, and, therefore, difficult to tabulate. The incidence of the main or, at any rate, the most conspicuous lesions is given in Table I.

TABLE I.—INCIDENCE OF THE MAIN STRUCTURAL ABNORMALITIES IN THE BRAINS OF 61 EPILEPTICS AND 57 NON-EPILEPTIC DEFECTIVES

Abnormality	Epileptic	Non-epileptic	Abnormality	Epileptic	Non-epileptic
Reduction in weight	53	54	Absence of corpus callosum	2	1
Ventricular dilatation	45	17	Atrophic changes associated with retrolental fibroplasia	2	1
Localized agenesis or atrophy	31	14	Pachygyria	2	0
Ulegyria	22	4	Fusion of frontal lobes	2	0
Cysts and cavities	18	7	Mongolism with cerebral abscess	2	0
Changes of uncomplicated mongolism	1	20	Mongolism with embolism	2	0
Localized or diffuse induration	18	1	Marked cerebellar sclerosis	2	0
Fibrosis of meninges	7	6	Lipidosis	1	1
Microgyria	6	0	Gargoylism	1	2
Tuberous sclerosis	5	0	Porencephaly	1	0
Calcification	3	3	Megalencephaly	1	0
Obstructive hydrocephalus	2	9	No gross abnormality	0	3
Arhinencephaly	2	3			

It will be seen from Table I that the commonest single abnormality was some reduction in the weight and size of the brain and this was often associated with corresponding ventricular dilatation. This reduction in size was usually at the expense of nerve cells and their processes while the number of glial cells seemed often to be relatively increased. Fibrous gliosis was a common feature in the cerebral cortex, the subcortical ganglia and, particularly, in white matter. It was not always associated with an increase in the number of glial cells. Cystic degeneration was also frequent, and there were, in addition, numerous developmental abnormalities.

The comparison of epileptics and non-epileptics in Table I has, of course, no statistical significance, except in respect of uncomplicated mongolism, and this will be referred to again. As already emphasized, epilepsy is very difficult to recognize in this group of patients. The figures, perhaps, suggest that structural changes, taken as a whole, are more severe in the epileptic group.

Another feature worth noting is that almost all the lesions were located in the cerebral hemispheres and cortex. They were also common in subcortical formation, e.g. basal ganglia, cerebellum, and brain-stem, but these were usually relatively slight and never present without other changes in the cerebral hemispheres. This material provides, therefore, no support for the concept of subcortical epileptogenic foci.

It may be claimed that all the brains of epileptic mental defectives present structural abnormalities and this view is in accord with the observations of Bateman (1936) and of earlier work on epilepsy in general (Scholz, 1930) as well as the recent findings of Murray Falconer (1953) in cases of temporal lobe epilepsy.

It has been suggested, however, by Scholz (1933 and 1936) that fits may in themselves be the cause of certain characteristic lesions, viz. loss of nerve cells in the cerebral cortex, and in the Purkinje layer of the cerebellum (Fig. 1) and in Ammon's horn of the hippocampus (Fig. 2), as well as fibrous gliosis in the hippocampus and along the surface and in the marginal layer of the cerebral cortex (Fig. 3) and cerebellum. He thought that these may be the only lesions in the so-called "genuine" or idiopathic

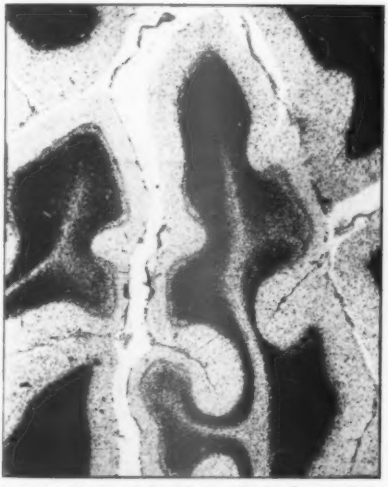

FIG. 1.—Loss of Purkinje cells in the cerebellum. Granular layer is also affected. Nissl. ×15.

FIG. 2.—Loss of nerve cells in the Sommer sector of the Ammon's horn. Nissl. × 2·7.

epilepsy. Such lesions were seen in some of the present cases, and might well have been the result of fits. They were not, however, particularly numerous, and never occurred alone, without other abnormalities. My material affords therefore no support for the existence of idiopathic epilepsy.

The relation of epilepsy to the constantly present lesions is not simple, similar structural changes occurring also in the brains of non-epileptic mentally defective patients. Moreover, one striking feature of epilepsy is that it need not be permanent, even though the lesions remain. Examples of epilepsy caused by metabolic disturbance without gross structural defect are, of course, also familiar.

Can it be, then, that the lesions are coincidental and unrelated to fits? Clearly not, since we all know how frequently the onset of fits may coincide with the development of a cerebral lesion. This is well illustrated in the present series in the case of mongols. 20 of the 24 mongols had no fits, and 4 did. Of the latter, 3 had Fallot's tetralogy, and 2 of these started having fits after the development of a cerebral abscess. The third patient with Fallot's tetralogy had fits for several years before death and the findings at autopsy were embolism of the left middle cerebral artery with softening of the territory supplied by it (Fig. 4). A similar case has also been reported by Kirman (1951). (The naked-eye appearance of the brain of the remaining epileptic mongol was that of uncomplicated mongolism, as seen in the 20 non-epileptic mongol cases.)

Thus we are faced with an apparent paradox which current knowledge cannot resolve: structural

abnormalities do and do not contribute to the occurrence of epileptic fits. It is highly probable that the difficulty lies in the omission of the all-important functional considerations. The integration, however, of structure and nervous function is still impossible on account of our lamentable ignorance of the latter; future progress will, no doubt, draw on developments in that field. But, for the time being, there is every reason to use the available fragmentary knowledge. In this connexion Pavlov's studies may be quoted. He demonstrated, for example, that the beneficial results of bromides given in carefully and individually graduated doses, depend on their effect of raising inhibition. He visualized cortical activity as a mosaic of constantly changing areas of excitation fringed by moving inhibitory barriers. A convulsive epileptic fit can therefore be interpreted as an explosive spread of excitation from the cortex to all parts of the nervous system and, particularly, the motor system, in which these barriers are overcome.

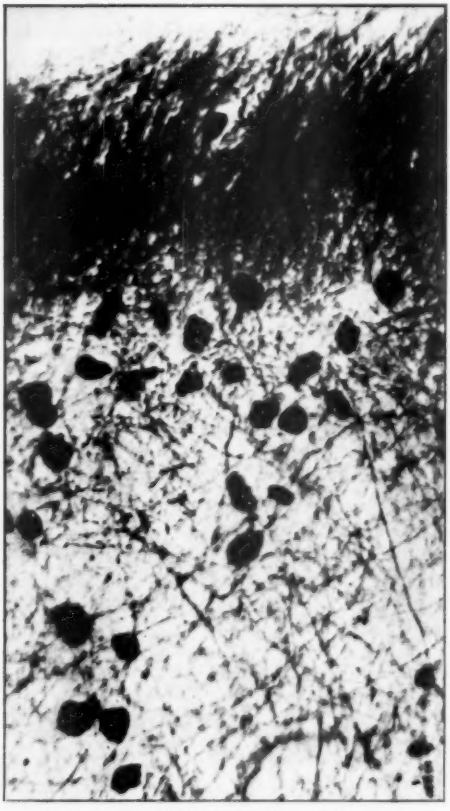

FIG. 3.—Marginal gliosis of cerebral cortex. Holzer. × 500.

Pavlov and his successors were more familiar with the behaviour of cortical inhibition than excitation. They demonstrated a whole range of conditions associated with inertness and abnormal spread of inhibition, e.g. hypnotic phases, hypnosis, schizophrenia, catatonia and shock. It is tempting to see in the various forms of epilepsy the excitatory counterparts of these pathological variants in the spread of inhibition. The most striking difference between the 2 sets of processes appears to be their duration: the rapidity of the convulsive epileptic fit compared with the relative slowness of most of the inhibitory pathological states.

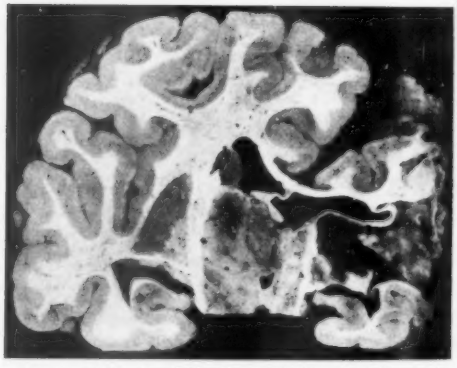

FIG. 4.—Softening following embolism of left middle cerebral artery. Coronal view.

It is finally necessary to consider to what extent morphological changes in low-grade mental-defective epileptics correspond with those of more intelligent epileptic patients. This question is, of course, difficult to answer, but it seems to me that processes in the former group of patients with a severely deranged brain, are often greatly magnified reproductions of similar events in more normal individuals.

The lack of attention given by most medical workers to the interesting field of mental deficiency is probably conditioned not only by the small expectation of therapeutic reward but also by the difficulty of recognizing familiar problems and phenomena in their grossly magnified, unaccustomed shape.

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Section of Radiology

President—J. Blair Hartley, M.D., F.F.R., D.M.R.E.

[*April* 30, 1954]

Three Years' Use of a Cobalt 60 Unit

By E. W. Emery, M.B., Ch.B., D.M.R.T.

University College Hospital, London

This is a brief report upon a Telecurietherapy Unit, using Cobalt 60 as a source of radiation, which has been in clinical use at University College Hospital for the past three years.

The Telecurietherapy Unit is of the pattern supplied by Messrs. Bryant & Symons & Co., Ltd., designed to accommodate 10 grammes of radium but using uranium shielding and applicators. In 1950, Dr. Gwen Hilton decided to exchange the radium already in use for Co ^{60}. In October 1950 the equivalent strength of Co^{60} to 10 grammes of radium, which is 6 c, was installed. This was later increased to 30 c and then to 60 c which has the equivalent strength of 100 grammes of radium. The amount of Co^{60} installed was limited by the protection afforded by the unit itself and the walls of the room in which it was to be used. No special building was used to house the unit; it was placed in a pre-existing room in the Radiotherapy Department. This room is 24 ft. × 18 ft. in size and has outside brick walls 18 in. thick, inside walls 24 in. thick. The Co^{60} itself is on a bobbin which is normally housed in a large lead safe in a corner of the room. It is blown via a delivery tube into the unit head (*see* Fig. 1) when required for treatments. It stays in the unit head during treatment time only, and at the end of each treatment is sucked back into the safe.

Maintenance.—The routine running of this unit requires very little maintenance, very few breakdowns occur, and the machine has only been out of action for very short periods of time. The only routine repair found necessary is the replacement of the felt washers which cushion the bobbin. These disintegrate under the influence of intense radiation and need replacing about every six months. Co^{60}, having a half-life of 5·3 years, decreases its activity almost exactly 1% per month, so that about every two years, renewal is advisable. This was an extremely simple operation. The delivery tube was disconnected from the unit head and this was taken through a window to the delivery lorry from Amersham. The bobbin containing the depleted Co^{60} was blown out to the lorry, the new bobbin, loaded at Amersham, sucked into the safe, and the tube reconnected to the unit head. The operation took minutes only, the unit being immediately available for use and treatment, and no handling of the radioactive material was required. This compares very favourably with the time and disturbance to change a tube in most deep X-ray therapy machines. As regards the cost of this unit, the total cost is only that of the cheapest 250 kV set available, and the Co^{60} itself costs £150 for 60 c. This cost, every two years, is no more and probably much less than the average cost of tube replacements of most therapy machines, so that this unit is cheaper and easier to run than most conventional deep X-ray units. It needs very little more space or protection, so that there are no great installation costs.

Protection.—It was found that using 60 c of Co^{60}, no added protection was needed other than a short brick wall to protect the entrance door of the room. Protection measurements gave quite low figures. The dose rate outside the room, near the control panel, is 0·1 of tolerance with the cobalt in the unit head, but twice tolerance while the cobalt is in transit between the safe and the unit head. The transit time is short, only a few seconds, so that no excess dosage is received by the operator of the unit. The effect on counting work with Geiger counters used near the treatment room is important. It was found that background counting was definitely affected, up to 50 yards distance in open air from the treatment room, but a much less distance if buildings were interposing. There is a physics laboratory within 20 yards of the treatment room where the background radiation is not altered owing to the protection afforded by the building.

Treatment applicators.—Co^{60} emits 2 gamma rays whose energies are 1·17 and 1·33 MeV, and has a H.V.L. of 10·6 mm. of Pb as calculated by Mayneord and Cipriani (1947) The half-value layer of this cobalt unit was measured by Merewether, Osborn and Wyard and was calculated to be 10·5 mm. of Pb. This unit, therefore, has an equivalent radiation to radium and supervoltage X-radiation of up to 3 MeV, and has a high output compared with conventional teleradium. At 8 cm. S.S.D. the skin dose rate was 180 r per minute. In a unit of this design the applicators, to give adequate protection, must be thick walled. The advantage of using uranium instead of tungsten

alloy for this purpose is considerable. Uranium having a higher atomic number, i.e. 92, to tungsten 74, has about 20% increase in absorption properties for radiation of H.V.L. 10·5 mm. Pb. In practice, this enabled the walls of the uranium applicator to be made 2 cm. less in diameter, still giving the same protection as tungsten applicators, and thus allowing greater ease of use in difficult sites. Due to the small size of the unit head and the great difficulty in obtaining uranium, only a limited number of applicators were available at first and the maximum field size was small, being 8 cm. × 6 cm., the minimum 4 cm. × 4 cm. The high dose rate of 180 r per minute at 8 cm. S.S.D. enabled the treating distances to be increased and still have adequate dose rate. In order to increase the range of applicators, a number of brass extension applicators were made to fit on each uranium applicator. These extension applicators were made to fit the field sizes obtained at varying treatment distances for each uranium applicator. (Fig. 1 shows the unit head and extension applicators, one of which is in position for treatment.) These thin-walled extension applicators greatly increased the ease of treating difficult sites and enabled glancing and angled fields to be used, which previously had been impossible, due to the thickness of the uranium applicators. They also provided a wide range of field sizes at very little cost, ranging from 4 × 4 cm. at 8 cm. S.S.D. to a maximum of 15 × 12·5 cm. at 20 cm. S.S.D. and at the same time served to delineate the beam and enable compression to be used in actual treatment.

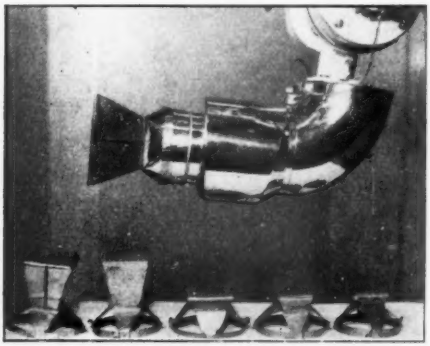

FIG. 1.—Unit head and extension applicator.

Depth and Isodose Curves.—Fig. 2 shows the comparative isodose curves measured by Wyard and

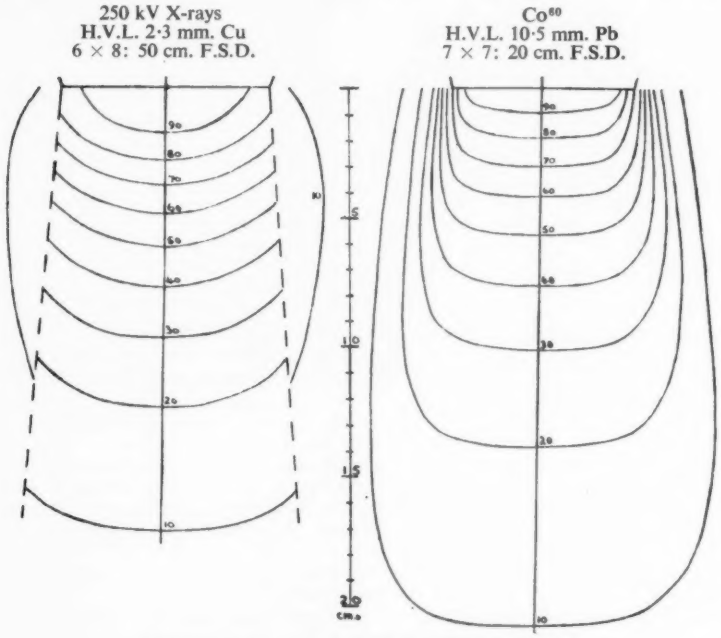

FIG. 2.—Comparative isodoses of 250 kV and Co^{60}.

Godfrey of similar field sizes of 250 kV, H.V.L. 2·3 mm. Cu at 50 cm. F.S.D. and Co^{60} at 20 cm. S.S.D. There is very little difference between them, the depth doses being a little increased and a little flatter, using Co^{60}. At 20 cm. S.S.D., the maximum field size is 15 × 12·5 cm. and with a skin dose rate of 20 r per minute. Similar depth dose curves are obtained to 250 kV therapy with the

added advantage of increased skin tolerance and decreased bone absorption due to the high H.V.L. of the radiation. Increasing the treating distances brings improved depth doses but, of course, rapidly decreasing dose rates. Theoretically, it is possible to treat at 100 cm. S.S.D. and to have depth doses similar to that obtained from megacobalt units, but the output would be too small to be practicable. Decreasing the S.S.D. down to its minimum of 8 cm., correspondingly decreases the depth dose and increases the skin dose rate to 180 r per minute. Fig. 3 shows the central axis depth dose curves

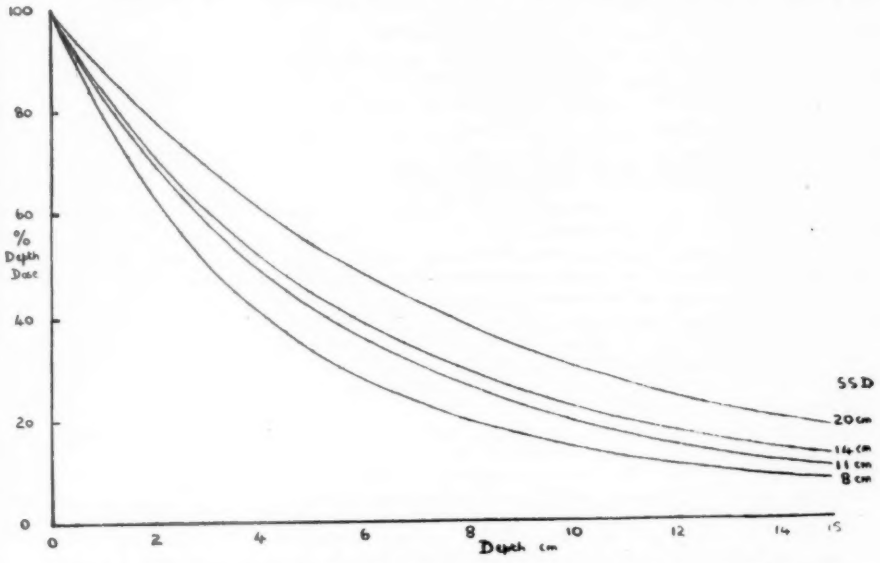

FIG. 3.—Cobalt beam unit. Central axis depth dose curves at varying treating distances.

obtained at the various treating distances which have been used. In all supervoltage X-ray therapy, the maximum dose is under the surface of the skin; with the radiation from Co^{60}, a build-up occurs a few mm. deep to the surface of the skin. Fig. 4 shows the depth dose measurements in the first few

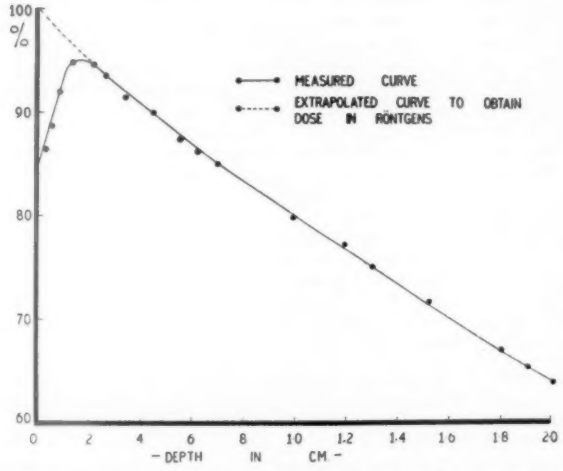

FIG. 4.—Central axis depth dose curve. (From Merewether, H., Osborn, S. B., and Wyard, S. J. (1952) *Acta radiol., Stockh.*, **37**, 464.)

mm. (Merewether *et al.*, 1952) showing the maximum dose to occur 2 to 3 mm. below the skin surface. The dose rate at the surface of a phantom is difficult to measure accurately with radiation of this energy. The skin dose was obtained indirectly by extrapolation, giving the broken curve of Fig. 4 which, if not the actual dose received at the surface of the skin, is a little greater than the build-up dose at 2 to 3 mm. deep. All skin dose rates have been correlated in this manner for all field sizes at all distances in order to prevent a false sense of security with skin doses which could not be accurate, and having an unknown greater dose just below the surface of the skin.

Clinical use.—This is a treatment unit which, because of its high H.V.L., the high output at short distances, and the variability of the depth doses which can be obtained, has been found useful for many purposes. During the last three years this unit has been used for the following types of cases:

(*a*) Superficial lesions such as large skin epithelioma and breast tumours.

(*b*) Lesions at short depths such as tumours of neck and mouth.

(*c*) Lesions surrounded by a quantity of bone, e.g. antral and pelvic tumours.

(*d*) Deep-seated tumours such as bronchus, œsophagus and bladder.

(*e*) Sites of poor skin tolerance to irradiation, such as groin, axilla, vulva, skin over bone such as clavicle, and the skin of young children.

(*f*) Sites of high risk of necrosis, e.g. carcinoma of the pinna and recurrent growths in pre-irradiated areas, e.g. internal mammary gland metastases and skin nodules following post-operative radiotherapy for carcinoma of the breast and recurrent malignant glands of the neck and axillæ.

(*g*) Because of the high dose rate at S.S.D.s resulting in short treatment times, a large number of patients can be treated daily by this unit. In practice we find that as many patients can be treated with this unit per day as with a 250 kV machine. Thus, besides radical treatments, there is time to treat many patients for whom palliation is all that can be hoped, and old patients who do not tolerate long treatment times.

This unit has been found useful for treating nearly all tumours in all sites of the body. Skin reactions, as expected, with radiation of H.V.L. 10·5 mm. Pb, are much less severe than with conventional deep X-ray therapy. The reactions have been rarely more than a brisk erythema, or a dry desquamation, with skin doses of 5,500 to 6,000 r in four to five weeks, even when given to groins and axillæ, and therefore the amount of treatment given to any tumour has not been limited by skin reactions. For example, a patient who had one groin treated by deep X-ray therapy elsewhere to a dose of 6,000 r in four weeks and had developed a severe ulcerated reaction which had taken three months to heal, was referred for treatment to his other groin. He received a similar dose with this unit, 6,000 r in four weeks, and developed only a brisk erythema which had completely subsided in three weeks.

With skin doses of 5,000 to 6,000 r in four weeks, the skin reaction reaches its maximum one to two weeks following the end of treatment. With protracted treatments of 6,000 to 8,000 r in six to eight weeks, the skin reaction reaches its maximum before the end of treatment and begins to subside immediately treatment is completed. With the dose levels which have been used, no severe blistering reaction has occurred. The most severe reaction to date has been a patchy, moist desquamation. [Colour slides were shown to illustrate skin reactions produced at varying dose levels.] There have not been, as yet, any cases of skin, bone or cartilage necroses, but enough time has not yet elapsed to exclude late necroses. One case of late subcutaneous induration has occurred due to the build-up dose beneath the skin surface. This type of reaction has been previously reported from the use of supervoltage radiation (Jones, 1948). The reaction occurred in a woman aged 70 years who had palliative treatment to an inoperable carcinoma of the breast. A skin dose of 5,500 r in three weeks was given. She had a brisk erythema with dry desquamation only. Eighteen months after treatment there was no telangiectasia, but there was marked subcutaneous induration which first became apparent one year after treatment.

The unit has been in use for three years, which is too short a time to provide adequate statistical results. The results at short treatment distances appear to be similar to those obtained by teleradium treatment. At 20 cm. S.S.D., the results appear to be an improvement on those obtained by conventional deep X-ray therapy because of increased skin tolerance and decreased bone absorption. At distances beyond 20 cm. results would be expected to begin to approach those obtained by megacobalt units and supervoltage X-ray units up to 3 MeV.

Conclusion.—The design of this unit is not ideal, having originally been designed for teleradium units. Many improvements could be produced by designing a unit specifically for use with 60 or more c of Co^{60}; nevertheless, the unit has proved to be extremely useful. It has been economical, and has required very little maintenance. This type of unit would be an asset in most radiotherapy departments, especially to those, which, through lack of space or finance, are prevented from acquiring new buildings or very expensive machines such as megacobalt and supervoltage units. In departments which already have supervoltage X-ray therapy, a cobalt unit of this type would be useful for short

distance treatments only. It also has the great advantage of using amounts of Co^{60} which are available and can be supplied and renewed within our own country at the present time.

ACKNOWLEDGMENTS

I would like to express my thanks to Dr. Gwen Hilton for her valuable help and advice, and also for her permission to publish this report.

My thanks are also due to Mr. S. B. Osborn for assistance with physical data.

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Treatment of Polycythæmia Rubra Vera with Radioactive Phosphorus

By D. VEREL, M.D., M.R.C.P.

POLYCYTHÆMIA RUBRA VERA has been treated with radioactive phosphorus for three and a half years at The London Hospital and I shall discuss the results in 18 patients. A great deal more experience is needed before we can predict confidently the duration of the response to therapy.

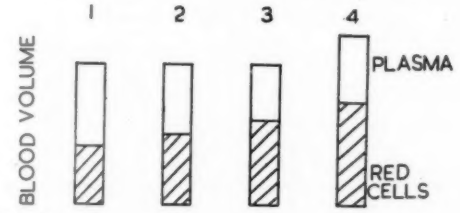
The blood-volume changes in polycythæmia rubra vera: Dr. G. W. Boden suggested that a study of the blood volume might explain why patients often claim great relief after administration of radioactive phosphorus while measurements of hæmoglobin or red cell count show little change. So far 27 estimations of blood volume have been made on 11 patients. I shall describe first a mild case. His red cell count was about 6,500,000, the total blood volume was normal, the venous hæmatocrit was 52% instead of the usual 45%. 5 mc of P^{32} were given by intravenous injection. Four months later the venous hæmatocrit was 45% and the blood volume was unaltered. After a year the figures are still normal, but the red cell volume has begun to rise, the venous hæmatocrit being 47%. In this patient the blood volume did not change and was within normal limits and therefore the findings in venous blood—the red cell count and hæmatocrit—provided an accurate index of the effect of P^{32}.

In a more marked case the initial blood volume was above normal and hæmatocrit was 67%. 5 mc of P^{32} caused a marked fall in red cell volume. The plasma volume increased and the total blood volume fell to normal limits. In this case the change in the total blood volume makes peripheral findings an inaccurate guide to the true extent of the improvement. Before treatment red cell volume in this patient was 180% of normal while the venous hæmatocrit was only 160% of normal. The change in total volume conceals about 20% of the alteration in red cell volume.

In a more severe case this effect may be very great, for example the third patient had severe polycythæmia. His blood volume was very high at 7 litres with a high red cell count and a hæmatocrit of 74%. He was treated initially by venesection, 4 pints being removed during one month. Two months later his blood volume had hardly altered but the hæmatocrit and red cell count had fallen markedly. His symptoms were little changed. He was given radioactive phosphorus and four months later said he felt he was back to normal. There had been a slight further fall in the red cell count and hæmatocrit but his symptomatic relief was presumably mostly due to the dramatic fall in blood volume which was now within normal limits.

Fig. 1 shows in schematic form the usual findings in this disease. It is based on the findings in the

THE EFFECT OF INCREASING RED CELL VOLUME



	1	2	3	4
Venous Ht.%	45	55	65	65
R.C.V. % ..	100	125	150	175
Plasma vol. ..	2·8	2·3	1·8	2·3

FIG. 1.—Composite diagram showing the changes in plasma and red cell volumes in polycythæmia rubra vera. For explanation see text.

AAA

11 cases investigated, and the normal blood volume is represented in column 1 as a rectangle, the red cell volume being 2 litres, the total volume nearly 5 litres and the hæmatocrit 45%. In a mild case (column 2) the hæmatocrit is raised and the total volume is normal. The normal total volume is usually maintained until the hæmatocrit is somewhere between 55% and 65%. Once the total begins to rise the venous blood picture no longer reflects the true state of affairs. For example, in this case if the venous hæmatocrit is 65% with the total normal (column 3), the red cell volume is 150% of normal. If, however, the total increases without further fall in plasma volume, the red cell volume is 175% of normal (column 4). I should say that this is a minimal figure for our cases. With a hæmatocrit of 65% I would expect the red cell volume to be at least double normal. This diagram, of course, presents the problem at its simplest. There are other factors; for example, some patients treated with radioactive phosphorus put on a great deal of weight and some of the changes observed are probably secondary to this.

These findings affect the interpretation of the red cell count and similar investigations made on the peripheral blood. They show that the laboratory findings will usually indicate the trend of events correctly, but that sometimes a marked fall in blood volume with little change in the red cell count may account for what seems a mysterious improvement in the patient's symptoms. The second point which comes out of these observations is that when the patient begins to relapse there may be little relation between the blood findings and the symptoms. We find that symptomatic relapse usually lags months behind the rise in the red cell count. This is understandable, for the symptoms seem to be related more often to the increase in blood volume than to the rise in the hæmatocrit, although this is not always the case.

Thirdly, I do not think that measurements of blood volume form a necessary part of the therapeutic control of the disease. In all our patients in whom the venous hæmatocrit was reduced to normal limits by effective treatment the total blood volume fell to within the normal range. It may be accepted that if the peripheral blood findings can be made normal then the total blood volume is also normal.

These observations have shown that in the management of a case of polycythæmia the patient's symptoms, however vague and improbable, should receive careful consideration. If the change in his symptoms seems to bear little relation to the laboratory findings it does not necessarily follow that the patient is imagining his complaints. It also means that assessing the success of treatment may be very difficult. When I came to review the series in an attempt to assess the value of the treatment I found that the lack of correlation between the clinical findings and the laboratory report was fully appreciated by those directing the treatment. In the end I concluded that the only single factor which took account of all the items and provided the least unsatisfactory way of assessing therapy was the length of time which elapsed before a further dose of radioactive phosphorus was thought necessary.

Table I shows the results of 8 cases which had no previous treatment. In 4 the results have been

TABLE I.—RESULTS OF TREATMENT WITH RADIOACTIVE PHOSPHORUS. NO PREVIOUS THERAPY

Case	Dose mc	Clinical response	Blood change	Duration of remission
L. H.	5	Good	Good	20 months
	5	Good	Good	21 months+
C. J.	7	Good	Good	4 months+
W. O'K.	7	Good	Good	8 months+
G. P.	7	Good	Good	9 months+
M. M.	3	Poor	Nil	4 months
	5	Good	Slight	12 months
	5	Good	Slight	27 months+
M. K.	6	Good	Slight	22 months+
V. C.	5	Fair	Poor	6 months+
S. L.	5	Poor	Nil	3 months+

good, both from the clinical and laboratory standpoint. In the fifth 3 mc had little clinical effect and no effect on the laboratory findings, while 5 mc have caused a good clinical remission with little blood change. In the sixth the clinical result was good, the laboratory one poor and in the last two the clinical response fair or poor and the blood change little or none.

Cases which have had previous deep therapy are shown in Table II. Here the results are very similar but it may be that these patients respond well to smaller doses of phosphorus; for example, the first patient had had six previous courses of deep X-ray therapy and responded well to 3 mc of radioactive phosphorus, a dose which we would expect to be ineffective in a previously untreated case. I have not shown in these tables the patients treated by other methods such as nitrogen mustard or phenylhydrazine as well as radioactive phosphorus. I would like to refer to one, who was treated for four years by venesection only—about 25 pints being removed in all. He is the only patient

TABLE II.—RESULTS OF TREATMENT WITH RADIOACTIVE PHOSPHORUS. PREVIOUS D.X.T.

Case	Dose mc	Clinical response	Blood change	Duration of remission
E. B.	3	Good	Fair	4 months
	3	Good	Fair	16 months
	3	Good	Good	6 months+
R. G.	5	Good	Anæmia	30 months+
A. D.	5	Good	Slight	10 months+
H. H.	5	Good	Fair	14 months+
J. W.	5	Fair	Poor	10 months
	7	Good	Good	13 months+

who has not responded to 7 mc of P^{32} and I suggest that the long period without any treatment which might depress his bone-marrow has allowed a great increase in red-cell-forming tissue and a consequent need for a very high dose. Lastly, Fig. 2 shows the duration of the response in patients

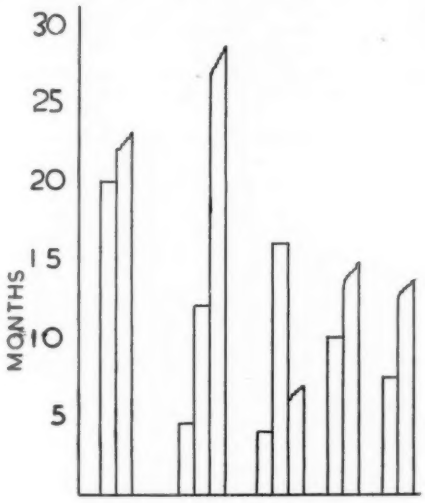


FIG. 2.—Increasing duration of remission in 5 cases of polycythæmia rubra vera after effective treatment with radioactive phosphorus.

who have had more than one therapeutic dose of P^{32}. In all cases where the follow-up is long enough the remissions have become longer. I think this has three possible explanations: the disease in these patients may be dying out, repeated effective doses of P^{32} may be curing the patients, or thirdly the indications of giving P^{32} may have changed. I do not think the last is the correct explanation and I would suggest that the disease in these patients is slowly being cured.

Some Experiences with Radioactive Phosphorus in the Treatment of Mycosis Fungoides

By F. E. NEAL, M.B., Ch.B., D.M.R.T.

Senior Registrar, Sheffield National Centre for Radiotherapy

THE purpose of this paper is not to suggest that radioactive phosphorus should be used as the treatment of choice in mycosis fungoides, but merely to describe some of the clinical and physical observations we were able to make on a small number of cases and to show that this method of treatment may be a useful therapeutic agent in the disseminated stages of this disease.

The localized tumours which occur can be satisfactorily treated or controlled for long periods by X-ray therapy. Invariably, however, a stage is reached when the condition fails to respond to therapy, visceral lesions develop, the patient's general condition deteriorates and progresses to a

marked cachexia before death supervenes. The two states in which we were particularly interested, were the so-called premycosic erythrodermia and those cases which present widely disseminated but frank superficial lesions of mycosis fungoides. The generalized nature of the eruptions in these two phases contra-indicates the use of orthodox X-ray treatment but it seems probable that the condition would respond to a more generalized form of therapy. In this connexion various chemotherapeutic agents have been used, e.g. antimony derivatives, cortisone and nitrogen mustards, with varying degrees of success. Since it is a radiosensitive condition, however, it would seem that good effect could be achieved with some form of internal radiation therapy.

For this purpose, radioactive phosphorus seemed to be the isotope of choice. It is known that increased uptake of P^{32} occurs in tissues exhibiting high metabolic activity and the β rays have a maximum range in tissue of 7–8 mm. Therefore, effective irradiation dosage could be delivered to the superficial lesions with the minimum irradiation of surrounding areas, provided that effective uptake was obtained.

The increased uptake of P^{32} occurring in the skin lesions in two cases of mycosis fungoides was demonstrated by Marinelli and Goldschmidt (1942) and various physical measurements on the lesions were described. It seemed that effective irradiation was obtained as the lesions were said to regress—although the clinical description was not complete. Low-Beer (1942) described a similar investigation on 5 cases of localized mycosis fungoides. Two failed to respond, but excellent effect was obtained in a third case in which a large tumour mass in the breast (treated by a combination of internal and external radiation) regressed and remained healed for several years. Laarsen (1952) described 2 cases of disseminated mycosis treated in this way in more clinical detail and obtained good palliation in both cases.

It was with the hope of repeating these encouraging results that we embarked upon this investigation.

Selection of Cases

The selection of cases presented very little difficulty. The condition is, fortunately, not common and we were willing to take on all-comers in the hope of achieving palliation. During the past year, 5 such cases have been treated by this method, 2 cases presenting premycosic erythrodermia and the others having widespread mycotic lesions.

In the first group of cases (the premycosic stage) both patients gave a history of recent onset of symptoms, the condition persisting in one case, in spite of treatment with cortisone.

The second group of cases were all of long standing and had failed to respond to previous treatments, including cortisone and X-ray therapy. In 2 cases the lesions involved the whole of the trunk and limbs, in the third case they were confined mainly to the face and scalp. The lesions were of the superficial weeping eczematous, or dry scaly type, and the patients were in a state of continual discomfort due to the exudation from the lesions.

Pruritus was the most prominent symptom in all cases. When first examined, there was no evidence of visceral extension in any case and pre-treatment blood counts and marrow examination were all within normal limits. Histological confirmation was obtained in all cases.

Treatment Technique

The treatment was carried out over a period varying from six weeks to six months. Radioactive phosphorus was given in the form of sodium hypophosphate and given in each case by intravenous injection. Since all the patients were hospitalized, this seemed to be the most convenient method of administration and eliminated the necessity of rigorous nursing precautions. The amounts of P^{32} given varied from 8 mc in six weeks, to 39 mc in twenty-three weeks. The smaller amounts were used in the treatment of the cases of premycosic erythrodermia.

No attempt was made to precalculate the dosage given. The amount given in each case was controlled by routine checks on the blood picture, the general condition of the patient and the progress of the local lesions.

No physical measurements were carried out on the 2 cases in the first group as no normal skin was available for comparison. 2 of the other cases were investigated in detail and the fifth case (which was treated rather more cautiously) was controlled on the results so obtained.

Physical Investigations

Injections of P^{32} were given at approximately monthly intervals and physical measurements were made for approximately fourteen days thereafter. The poor general condition of the patients necessarily limited the number of investigations performed, as we wished to subject them to the minimum of biopsies and venepunctures.

A specific lesion was chosen, biopsies being taken from this and a corresponding area of normal skin on 2–3 occasions after each injection. The tissue obtained was weighed, dissolved in concentrated hydrochloric acid and measurements were made in an M. 6 liquid counter compared against a standard taken from the original injection of P^{32}.

A similar technique was used to obtain values for the blood and bone-marrow (Table I).

TABLE I.—DOSES CALCULATED FROM PHYSICAL MEASUREMENTS MADE FOLLOWING REPEATED INJECTIONS OF RADIOACTIVE PHOSPHORUS THERAPY SHOWING GREATER UPTAKE IN LESION THAN IN NORMAL TISSUES

DOSES IN TREATMENT OF MYCOSIS FUNGOIDES WITH P^{32}

Patient	Date	mc. given	Dose (rep.) Lesion	Skin	Blood	Bone-marrow
Miss P. A.	27.5.53	5·0	95	29	18	36
„ B.	26.6.53	4·0	71	33	27	12
„ C.	23.7.53	4·0	72 29	13	—	—
Mr. W. A.	27.5.53	7·0	147	40	18	20
„ B.	26.6.53	5·0	107	29	26	20

At a later stage in the treatment, measurements were made of superficial lesions and corresponding areas of normal skin, using a modified G.M.4 end window counter, having a brass housing with a collimating cylinder 1·5 cm. diameter. This allowed exact repositioning of the counter on different occasions. By this means isodose contours were obtained. The counter was calibrated against a solution containing a known amount of P^{32}. Some difficulty was experienced in obtaining exactly reproducible results, due presumably to the varying amounts of incrustations over the lesion on different occasions (*see* Fig. 1).

MYCOSIS FUNGOIDES

Concentration of P^{32} in tissues after injection of 4·0 mc.

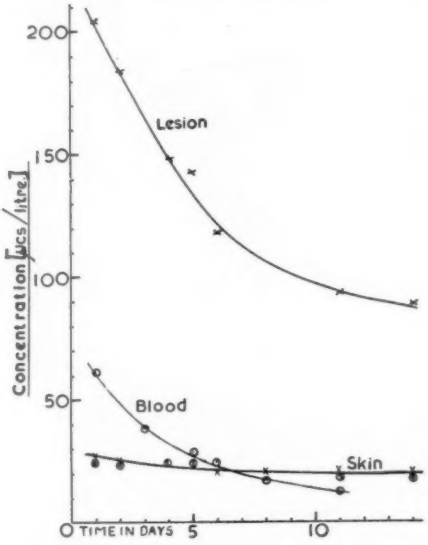


FIG. 1.—Graph of results obtained with end window counter showing greater uptake in lesion than in normal skin.

In both cases there was found to be an increased uptake in the lesion compared to the uptake in normal skin. The relative amount being three to seven times greater in the lesions. The uptake in the blood and bone-marrow was comparable to the uptake in normal skin. It should be emphasized that the doses shown are only an approximation, and apply only to the surface layers of tissue, since the half-value layer of the P^{32} beta rays in tissue is only of the order of 1 mm. The half-life of the P^{32} in the lesions was considerably shorter than that in normal skin and blood, presumably due to the increased metabolic activity in the lesion. To avoid errors due to increased vascularity in the neighbourhood of the lesions, vasodilation was produced over a small area of normal skin. No increase in counting rate (greater than 2–3%) was observed in this area as compared with the normal skin.

The dose to the blood and bone-marrow was in all cases relatively low, but in one case, marked depression of the platelet count was noticed (*see* Fig. 2). In all other cases the blood picture remained within normal limits throughout treatment.

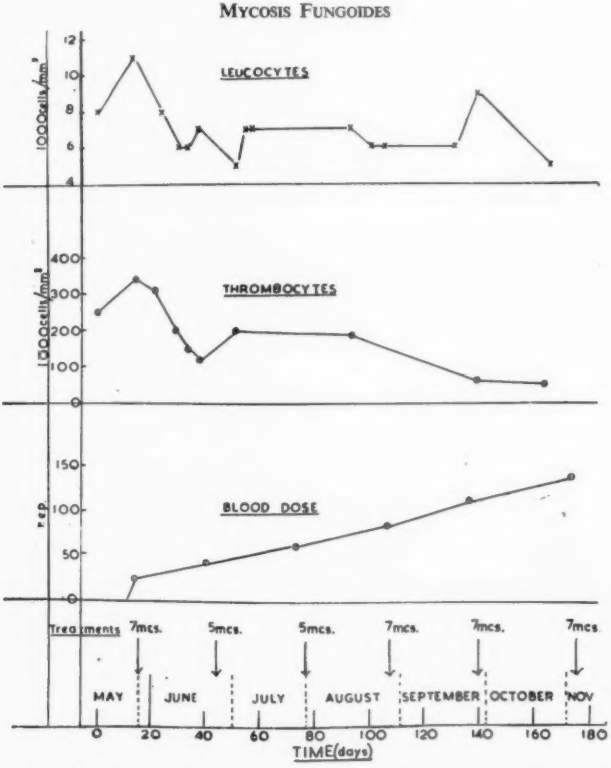


FIG. 2.—Showing marked depression of platelet count after repeated injections of radioactive phosphorus (39 mc in six months).

CLINICAL RESULTS

In all cases there was a subjective improvement and a temporary or permanent relief of pruritus. Of the 2 cases presenting with erythrodermia (*see* Table II) 1 improved rapidly, and three months

TABLE II.—RESULTS OF RADIOACTIVE PHOSPHORUS THERAPY IN FIVE CASES OF MYCOSIS FUNGOIDES

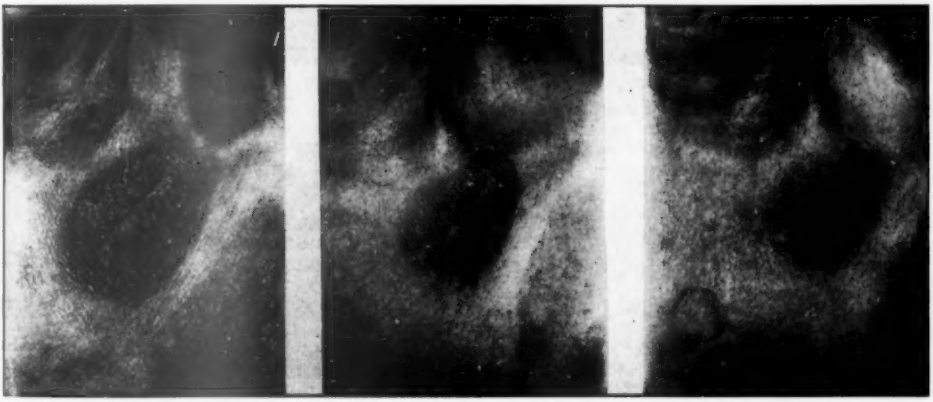
		Age	State	Previous treatment	Response to P 32	Dosage
I	Male	65	Premycosic erythrodermia	Cortisone	Complete relief of symptoms	8 mc in 6 weeks
II	Male	73	Premycosic erythrodermia	None	Slight improvement in pruritus	15 mc in 6 weeks
III	Female	63	Disseminated lesions	X-rays	Marked improvement for 4 months	29 mc in 23 weeks
IV	Male	67	Disseminated lesions—Face mainly and scalp	X-rays Cortisone	Gradual improvement of scalp and face	39 mc in 23 weeks
V	Female	32	Disseminated lesions	X-rays Cortisone	Improvement in pruritus	11 mc in 23 weeks

after commencing treatment was symptom free and the skin had returned to normal. It has remained so, for the past year. The second case did not respond well. There was a little relief of pruritus but the skin condition did not change and treatment had to be abandoned because of intercurrent illness

In the second group of cases, one patient did not respond well (*see* Table II). A little temporary relief of pruritus was obtained but the skin lesions did not change. A gradual improvement was noticed in the case presenting with lesions on the face and scalp and this improvement has been maintained although further lesions have developed on the trunk and lower limbs (*see* Fig. 3). The lesions in Case III began to fade three weeks after commencing treatment and continued to improve for four months (*see* Figs. 4, 5 and 6) after which further lesions occurred which persisted in spite of therapy. The patient refused further hospitalization and died of intercurrent infection.

(*a*) (*b*)

FIG. 3. (*Case IV*).—Mycosis fungoides—superficial lesions of face and scalp. (*a*) Before treatment. (*b*) Six weeks after starting treatment. The œdema of the face is less and the lesions have regressed to some extent.



(*a*) (*b*) (*c*)

FIG. 4 (*Case III*).—Superficial lesion of left shoulder showing regression during treatment. (*a*) Before treatment. (*b*) Six weeks after starting treatment. (*c*) Three months after starting treatment.

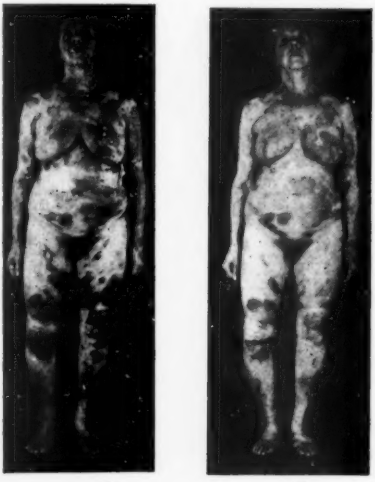
DISCUSSION

The natural history of the disease—characterized by spontaneous regression and recurrence of lesions—makes it difficult to assess adequately any form of therapy especially on a small number of cases. However, increased take-up of radioactive phosphorus was demonstrated in the lesions and approximate doses calculated.

The improvement of the lesions in 3 of the cases under consideration cannot be ignored completely. The amount of radioactive phosphorus given was not as large as was originally intended, but must have been sufficient to give adequate irradiation to the lesions for regression to have occurred. Even with these relatively small amounts of P^{32}, marked depression of the platelet count was produced in one case. Laarsen (1952) obtained satisfactory palliation in one case with approximate lesion dose of 500 r e.p. but suggested that it would be improbable that smaller doses than this would have any useful effect. In this series the amount of phosphorus given was smaller and given over a larger period of time, yet regression of lesions occurred. Since serious hæmatopoietic disorders can arise

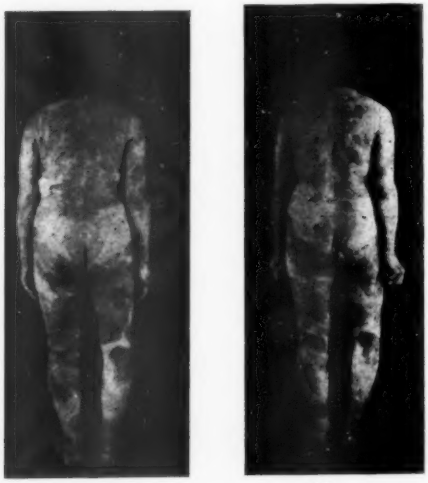
with this form of therapy, it would seem that the lower dosage rate is perhaps a preferable form of therapy. The temporary or permanent relief of pruritus obtained is an important fact. This is a common symptom in all forms of malignant skin disease and radioactive phosphorus may prove a useful method of relieving this distressing condition.

It should be emphasized that the aim of this investigation was to produce palliation in the first instance. For localized lesions X-ray therapy remains the treatment of choice, but for the more widespread forms of the disease P^{32} would seem to have a useful effect in some cases.



(*a*) (*b*)

FIG. 5 (*Case III*).—Showing improvement in lesions on trunk and limbs. (*a*) Before treatment. (*b*) Three months after treatment.



(*a*) (*b*)

FIG. 6 (*Case III*).—Showing improvement of back and limbs. (*a*) Before treatment. (*b*) Three months after treatment.

SUMMARY

The treatment of 5 cases of disseminated mycosis fungoides by multiple injections of radioactive phosphorus over a long period is described. The physical measurements and data obtained are recorded and the palliative effect likely to be obtained from this form of therapy is briefly discussed.

Acknowledgments.—My thanks are due to Mr. J. C. Jones, M.A., A.Inst.P., Assistant Physicist, who undertook the whole of the physical measurements, to Dr. J. Walter for the original suggestion and for much helpful advice, to Mr. G. W. Blomfield for helpful criticism and encouragement, to Mr. N. Morton, M.S.R.(C.T.), Radiography Tutor, for preparation of photographs and slides, and to Mrs. R. Martin for preparing the manuscript.

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Section of Surgery

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*December* 2, 1953]

DISCUSSION ON HEAD INJURIES IN CIVIL PRACTICE [*Abridged*]

Mr. Walpole Lewin (Radcliffe Infirmary, Oxford):

The Management of Acute Head Injuries

Published statistics in England and Wales since 1950 indicate that just over 70% of the fatal road accidents are associated with a head injury, and that there is an annual death roll in England and Wales of about 3,500 from this cause alone. In addition there are 25,000 patients who are discharged from hospital annually following head injuries in road accidents severe enough to have detained them. As shown in Table I, this is not our total commitment; about a quarter of head injury cases admitted to hospital do not result from road accidents. One may conclude that the total number of head injuries requiring in-patient hospital treatment annually in Great Britain is at least 35,000. This is almost certainly a conservative estimate, for Schorstein, Robertson and Fletcher (1952), from a Glasgow survey, concluded that 1,200 head injuries require in-patient treatment annually per million population. Such numbers and the mortality rate indicate the size and gravity of the problem.

CASE MATERIAL

The following remarks on the acute stage of head injury are based on the management of 1,750 consecutive cases of acute non-missile head injuries admitted to the Accident Service of the Radcliffe Infirmary, Oxford, in the five years November 1948 to November 1953. They include all the patients admitted to the hospital directly from the accident together with 280 patients transferred from other hospitals for further treatment.

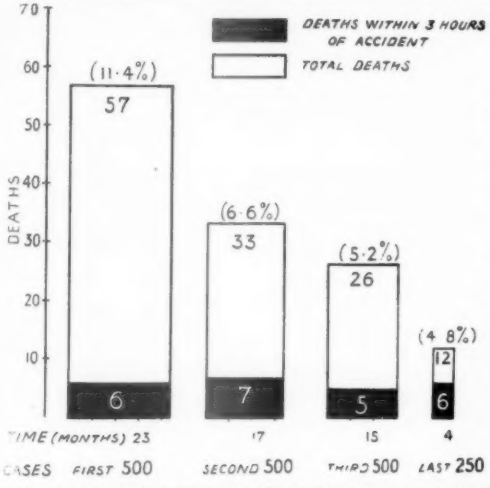


FIG. 1.—Mortality rate in 1,750 consecutive non-missile head injuries (7·3%).

The overall mortality was 7·3% weighted by the higher mortality (12·2%) among the many serious cases in the transferred group (Fig. 1). Even in an unselected series such as this the rate will depend on many factors; for example the speed with which the gravely injured patients reach hospital and whether, as has been done here, those patients who die in the admission room before reaching the wards are included. There has been an encouraging fall in the mortality rate of the last 750 cases to about 5%, even though, as Fig. 1 shows, the incidence of patients who were in coma from the time of the accident and who died within the first three hours after the accident actually rose in recent months. The steadily increasing number of head injuries is also shown.

All these patients were treated within the Accident Service of the hospital and the advantages of such an arrangement will be referred to later.

PREVENTION

Prevention is so important that even though it cannot be considered in detail at this juncture it should be mentioned at the beginning of any discussion on injuries. Doctors see casualties from their own particular angle and from time to time may be able to add their contribution, however small, to the prevention of some accidents.

Who are the people involved in these accidents? Table I gives an analysis of 1,000 consecutive head injuries admitted direct to this hospital from the scene of the accident. The high incidence of cyclists betrays perhaps the City of origin, but since the Radcliffe Infirmary admits all the injuries

occurring in the city and immediate area it gives some idea of the relative distribution of head injuries among road users and others. It also emphasizes the error of pitting one road user against the other as the principal miscreant. We are all in this together. Moreover, many accidents occur at home or at work, and some in circumstances which are as deserving of the indignation which is so frequently levelled against the jay walker or the luckless motor cyclist. In listening to the accounts of these accidents one is, of course, hearing only one side of the story, but the frequency of defective rear lighting being blamed as the cause of the collision, the children who fall out of moving cars, the pedestrians who are knocked down from behind and the elderly people who fall downstairs at home, suggest that there are several ways by which some of these accidents could be prevented with a little more care, quite apart from the often discussed topics of speed and alcoholism.

TABLE I.—ACCIDENT DETAILS IN 1,000 CONSECUTIVE HEAD INJURIES (DIRECT ADMISSIONS)

Type	Recovered	Died	Total
Car	116	9	125
Motor cycle	208	16	224
Push cycle	219	14	233
Pedestrian	142	21	163
All road accidents ..	685	60	745
At work	45	6	51
At home	58	4	62
At play	83	0	83
Other (assault, &c.) ..	58	1	59
	929	71	1,000

Protective head gear has been designed principally for the motor cyclist. Table I shows that despite the fact that there are four times as many cars on the roads as motor cycles, and many more push cycles, yet the motor cyclist is near the top of the list in head injury figures. He runs a considerable and special risk of head injury. Thus in 1950–52 in our hospital fourteen motor cyclists died as a result of their injuries and all but one had sustained a major head injury. The value of a suitably designed crash helmet was amply demonstrated by the Army in the War (Cairns, 1941, 1946; Cairns and Holbourn, 1943). Their value in the Army can still be shown in another way. During 1953 at the Military Hospital for Head Injuries, Oxford, of the last 20 motor cyclists admitted with head injuries, 17 sustained their accidents off duty, usually at the week-ends, and when they were not wearing crash helmets. Civilian motor cyclists are beginning to wear crash helmets although so far the number wearing them is too small to affect the morbidity or mortality figures from any one hospital. It is encouraging to see the renewed interest in this protective gear but it should be remembered that there is much more experimental work required to determine the best type of helmet for civilians, and one must avoid the use of unsuitable materials in order to reduce costs, or the sacrifice of essential features for cosmetic reasons.

Car drivers and their passengers may sustain head injury by hitting the dashboard or some projection, and in the future car manufacturers may have to consider other materials and a fresh design for the controls, to minimize this risk.

FACTORS IN THE MORTALITY RATE

Since about 70% of the deaths from head injury occur within the first twenty-four hours after injury, and many of the others in the early days afterwards, attention must always be focused on this period if the mortality rate is to be reduced significantly.

Some deaths could be prevented by the earlier recognition and treatment of intracranial hæmatomas and of cerebral compression from other causes, by the maintenance at all times of adequate airway, and, in patients who remained unconscious, by attention to the nutritional requirements and to the metabolic disorders which may arise.

Intracranial hæmatomas.—Intracranial hæmatomas, extradural, subdural and intracerebral, do not occur in more than 6% of head injuries, but they are important since, untreated, they are usually fatal. Of 1,750 consecutive head injuries admitted over the last five years, 102 patients had an intracranial clot, and 10 of them more than one (Table II). These figures include those cases, 4 in all,

TABLE II.—INTRACRANIAL HÆMATOMAS IN 1,750 CONSECUTIVE CASES OF HEAD INJURY

Hæmatoma	Recovered	Died	Total
Extradural	36	10	46
Acute subdural (less than 14 days after injury) ..	24	17	41
Chronic subdural (more than 14 days after injury)	6	0	6
Intracerebral	6	3	9
Total	72	30	102*

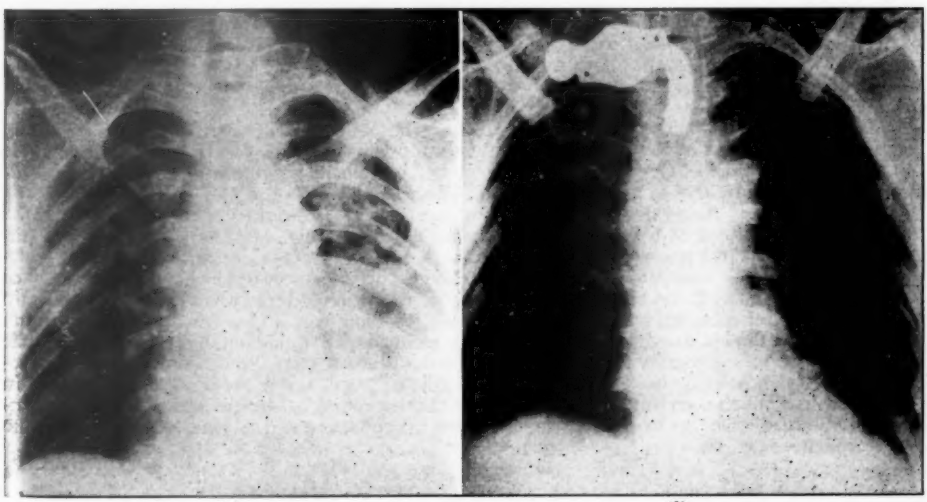
*Includes 4 cases diagnosed at autopsy.

which were diagnosed only at autopsy. Although 72 of the 102 patients recovered, there were many deaths. In some, and particularly with the acute subdural hæmatomas, the associated brain injury was the primary factor responsible for death, but in others delay in the evacuation of the clot or secondary complications was the main cause. The fact that 36 of the 46 patients with extradural hæmatomas in this series recovered was due largely to having the majority of these patients under observation from shortly after the accident so that it was possible to diagnose and operate on them early, and at a time, for example, when the pupils were still equal and reacting. Another factor was that the geography of the Oxford region allowed in many instances rapid transfer of suspected cases to the Centre. The operative and post-operative difficulties of many of these patients with hæmatomas suggest that where possible it is desirable to transfer them to a neurosurgical centre, but this has to be weighed carefully against the time factor involved; among these patients there is a small number where coma is of early onset and the signs rapidly progressive, and in these patients operation, to be effective, must be carried out at once by the surgeon on the spot. The following case record illustrates the type of case demanding immediate surgery.

This patient of 45 years was knocked off his motor cycle and came into hospital within half an hour of the accident. He had been unconscious for a few minutes but on admission was talking and at the most was mildly confused only. There was a small right parietal scalp laceration and it was noted that he was very restless and complaining of headache. The principal injury, however, was a compound fracture of the right tibia and fibula with impairment of the blood supply to the foot, and arrangements were made for its immediate treatment. Whilst having the leg X-rayed, it was noted that the patient was drowsier and within minutes he was stuporous and the right pupil had dilated. This was less than two hours after the accident. The patient was taken to the theatre immediately (where an emergency craniotomy set is kept ready sterile), and a large extradural hæmatoma was evacuated. The leg was also treated and the patient made an uneventful recovery.

The airway.—Whatever else is done, the unconscious patient should have an adequate airway at all times. In most cases this may be accomplished by suitable posture, simple airways, and suction. In others tracheal toilet, and, in selected cases, bronchoscopy may also be required.

In a small group of patients we have also found that tracheotomy, provided it is not left until too late, can be a life-saving procedure. These patients are usually in coma for long periods; cerebral compression, if present, has been relieved as far as is possible and for a variety of reasons which have been discussed elsewhere (Lewin, 1953) the simpler measures referred to above have proved inadequate to maintain the airway. So far we have performed twenty-four tracheotomies. This number indicates that the operation is not required often; but the fact that of these severely injured patients, 8 have finally recovered, had the tracheotomy closed and returned to their homes or work, suggests that it has a place in treatment. In a further 4 patients the chest problem was adequately dealt with by tracheotomy, which was subsequently closed, although the patients died later from other effects of the head injury. Fig. 2 illustrates the beneficial effects of a tracheotomy. The response to tracheotomy in these desperate cases is further evidence of the importance of extracranial factors in the mortality of head injuries.



(*a*) (*b*)

FIG. 2.—To show resolution of bronchopneumonia after tracheotomy. Radiographs taken (*a*) five days *before* tracheotomy, and (*b*) eight days *after* tracheotomy.

Metabolic disorders.—The need, in the unconscious patient, to maintain a satisfactory fluid balance is paramount but even in circumstances where this is attained, a recent biochemical study of 76 patients unconscious for longer than twenty-four hours following a head injury showed that nearly a quarter of them developed major metabolic disorders, which by comparison with their occurrence in other circumstances are attended by a high mortality (Higgins *et al.*, 1954). Chloride imbalance, hyperglycæmia, alkalosis, and uræmia may all develop. Some of these are correctable by early treatment. Thus in 12 of 18 such patients in the series reported, metabolic disorders were corrected with recovery of 7 of the patients. The evidence so far suggests that attention to the metabolic requirements of the unconscious patient should form part of the basic management of the acute head injury and that it is a factor in lowering the overall mortality.

Planning for Head Injuries

In planning for the treatment of head injuries, there are general and special considerations. Two of the main requirements of the early stages are essentially general ones. One is good nursing with careful observation of all head injuries both mild and severe, which with attention to the airway and the patient's nutritional needs will lower the mortality significantly. These cases should be considered to be in the same need of acute observation and management as, for example, the abdominal emergency. The second requirement is a careful, and if necessary repeated, examination to ensure that, particularly in the unconscious patient, other injuries are not overlooked. 30% of head injuries have other injuries elsewhere, and their correct management and order of treatment may decide the issue.

These observations have a general application to all head injuries wherever they are treated, but the 10% or so of patients who develop intracranial complications, and other patients who at some stage give rise to anxiety, require further discussion. There are cogent reasons for believing that in order to lower the mortality in these complicated cases, they should be transferred wherever possible to a neurosurgical centre. Not only are there several operative complications of intracranial hæmatomas, but there are other problems which arise in the acute stage after head injury which may require full neurosurgical facilities. The number of such cases is not prohibitively high; there are now many neurosurgical centres in the country so that at least in some areas a restricted service of this kind, as in fact is already the case in many instances, should be possible. To be effective, however, there are certain provisos. The surgeon at the peripheral hospital should be able, if he wishes, to transfer a case which is causing him anxiety without delay, even though in some instances no operation or other special measure proves necessary, and he should also be encouraged to send the case early. It is useless to wait until the patient is deeply comatose and the pupils fixed and dilated. Then transport must be easy, and this will, of course, vary considerably with each region. Another important factor in success is that it should be a two-way service and the sending hospital should be able to receive back the case as soon as special treatment is finished; only in this way can a service be maintained on the very limited neurosurgical beds. There are many calls on these beds, but neurosurgical help should be available in the management of head injuries which can have such a high recovery rate and return to a useful working life. Where an Accident Service exists there is much to be said for having the head injury service contained within it. The quicker turnover in general traumatic work allows greater elasticity, and the advantages to the patient with multiple injuries are, of course, immediately apparent.

With the exception of the small group of rapidly developing extradural hæmatomas previously referred to, where operation by the surgeon on the spot is demanded, and those patients with multiple injuries, head injury patients travel well. In this series 280 patients have been transferred from other hospitals with a mortality in this group of serious injuries of 12·2%.

For those parts of the country where such a regional scheme is impracticable, or where for other reasons such as outlined above, transfer is not possible, or desirable, then the general surgeon has to shoulder the major responsibility in the acute stage. One should consider in the future post-graduate facilities for those surgeons who require further experience in head injury work as part of their general training. It has been suggested that periods of one to three years are required to gain the necessary experience, but I believe that a period of six months in a busy head injury unit, taking part at the same time in the general work of the Accident Service should equip a man with the basic essentials. This means that in some centres at least the neurosurgeon should be able to accept responsibility for all the acute head injuries in his immediate area as well as for the special cases sent in from elsewhere. Such a service would allow for the basic training of the young surgeon and neurosurgeon. It also enables the whole problem to be seen in proportion and, as demonstrated during the war, stimulates research.

Conclusion

It is apparent that the number and mortality of head injuries call for the combined services of the general surgeon and the neurosurgeon, and that by managing many of the difficult cases together the mortality rate could be lowered. Much can be done with our existing facilities in this way, and

in addition young surgeons in their training should have the opportunity of short-term experience in head injury work. The overall mortality of those cases sufficiently severe to be admitted to hospital can be reduced to well under 10% and even though this may be partly achieved by further attention to intracranial complications, the management of the many extracranial factors will also prove as important.

ACKNOWLEDGMENTS

I wish to thank Mr. J. C. Scott, Director of the Accident Service, for his advice and encouragement in this work; and the Road Research Laboratories, Harmondsworth, Middlesex, and the Royal Society for the Prevention of Accidents for help in the preparation of the accident statistics.

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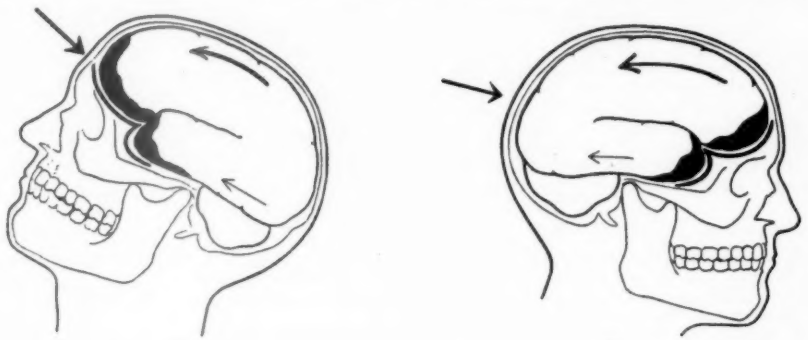
Mr. John Gillingham (Department of Surgical Neurology, Royal Infirmary, Edinburgh):

Types of Head Injury

A clear concept of the pathology of unconsciousness in blunt head injury will ultimately guide us to the proper management of these difficult surgical problems. There is still much to learn about the common mechanisms of fatality in these injuries and the place of surgery in dealing with them. Perhaps it is the insecurity of our knowledge and the uncertainty of our approach to the injured comatose patient that sometimes mean fatal delay in the evacuation of clot or decompression for brain swelling.

In civil practice there are two types of blunt head injury, crush injury in which loss of consciousness is unusual, and the more common and important acceleration or deceleration injury which is usually associated with concussion. Crush injuries are relatively infrequent and they will not be considered further in this discussion.

Acceleration and deceleration injuries are essentially similar in their effect upon the head. In the case of direct injuries, compression distortion of the skull is maximal at the site of the blow, and immediately on the opposite side, there is a tensile type of deformation. If fracture occurs, it may be immediately subjacent to the site of the injury or, because of distortion, some distance from it (Gurdjian and Lissner, 1944). It is this type of skull distortion, with or without skull fracture, which is responsible for tearing of the middle meningeal vessels, the usual cause of extradural hæmatoma.



(*a*) (*b*)

FIG. 1.—The common situation of contusions and lacerations in acceleration head injury (after Courville).

Underlying injuries of the cerebral cortex and its blood vessels are dependent on the severity of these deformations, probably from local negative pressure effects, and *coup* and *contre-coup* injuries are partly accounted for in this way. The brain substance as a whole is relatively incompressible and therefore subjected to transmitted distortion stresses which, in the more severe injuries, are responsible for the scattered hæmorrhages in the white matter that are occasionally seen at autopsy.

However, the common source of brain injury is from rotational and linear acceleration forces which occur when the head is suddenly accelerated or decelerated in space (Holbourn, 1943). As we shall

see later, these forces determine direct injury to the brain and its superficial blood vessels, the cortical veins and arteries. Of greater significance is indirect injury to the important basal brain structures, the hypothalamus and basal ganglia, from stretching of the perforating branches of the circle of Willis which occurs as a result of the sudden cerebral displacements of rotational and linear acceleration forces.

The commonest sites of laceration and contusion in acceleration and deceleration injuries are, as one might expect, the inferior surfaces of the frontal lobes and the anterior aspects of the temporal lobes, in the region of the lesser wing of the sphenoid; the result of positive pressure injury in forward rotations and negative pressure injury in backward rotations (Fig. 1).

The extent and severity of the lesions are, of course, in proportion to the severity of the acceleration injury. Cerebral lacerations of this type, even in severe injury, are seldom more than 1 cm. in depth and, as we know from war experiences of similar superficial penetrating brain wounds, are not in themselves significant as a cause of disturbed consciousness or death. Nevertheless they are important as a potent source of complication in severe head injury, namely subdural hæmatoma, intracerebral hæmatoma, and contusional brain swelling. Subdural and intracerebral bleeding arise usually from torn veins, and to a less extent from tearing of the more robust arteries, at the site of laceration (Fig. 2). Another potent, although less common, source of subdural bleeding is from the superior

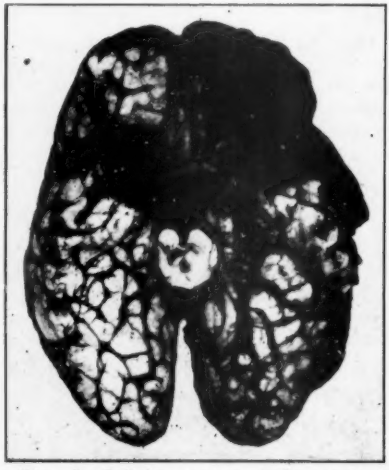


FIG. 2.—Inferior aspect of the cerebral hemispheres showing severe fronto-temporal lacerations and the remains of a large subdural hæmatoma on the left. There is a secondary mid-brain hæmorrhage from unrelieved raised intracranial pressure from clot.

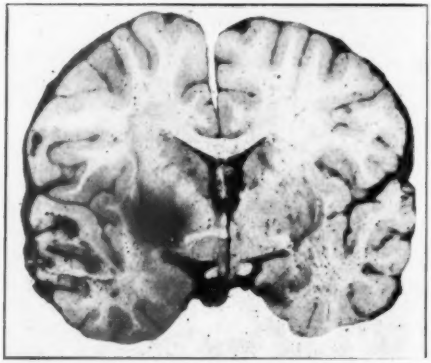


FIG. 3.—Coronal section of the brain at the level of the anterior commissure to show a hæmorrhagic lesion of the right lentiform nucleus with surrounding swelling following deceleration injury of the head.

cerebral veins which pass from the supero-medial border of the cerebrum to drain into the sagittal sinus. In acceleration and deceleration injuries they may be suddenly stretched and torn by rotation of the brain within the dura. Once bleeding begins, it is maintained, and indeed hastened, by the high intracranial venous pressure which is associated with impairment of the airway, so often seen in the deeply unconscious patient.

Acute subdural hæmatomas (those which show themselves within hours of injury as opposed to the subacute variety which show themselves days after injury) are caused by severe acceleration or deceleration injuries and are, in our experience, associated with a very high mortality rate in this group of complications. Although in some cases operation for evacuation of clot was performed too late, it seemed that some other major lesion must have been responsible for such grave consequences.

It is said that the lesser wing of the sphenoid by resisting movement of the cerebral hemispheres in this region largely protects the circle of Willis and its important perforating branches to the basal nuclear region of the brain from injury. However, there is clinical and pathological evidence which does not entirely support this view.

For example, Fig. 3 shows a coronal section of the brain of a boy of 5, who succumbed four days after a right parieto-occipital deceleration injury, never having regained consciousness. Severe bilateral fronto-temporal lacerations in the neighbourhood of the lesser wing of the sphenoid were present, indicating

a severe degree of displacement of the hemispheres at the time of injury. In this section there is hæmorrhagic infarction of the right lentiform nucleus and some surrounding ischæmic brain swelling. Perforating branches of the middle and anterior cerebral arteries can be seen extending into the clot and it would seem that this lesion has arisen from stretching and tearing of these vessels during sudden posterior rotation of the hemispheres at the time of injury (cf. Fig. 5 for anatomical distribution of the perforating vessels).

A similar lesion of the basal ganglia, to some extent bilateral, is evident in the following coronal section of the brain of a man of 27 who died twenty-four hours after injury (Fig. 4). In his case, division of the corpus

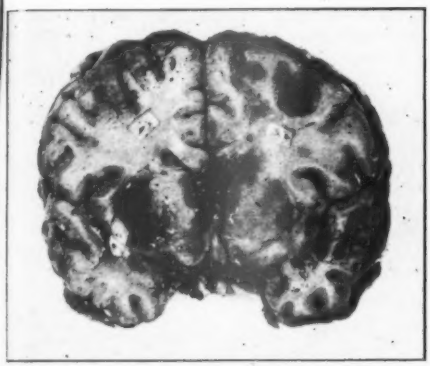


FIG. 4.—Coronal section of the brain following severe deceleration injury. The corpus callosum has been divided by the falx and the septum pellucidum ruptured. There is hæmorrhagic infarction of the right basal ganglia and to a less extent also on the left.

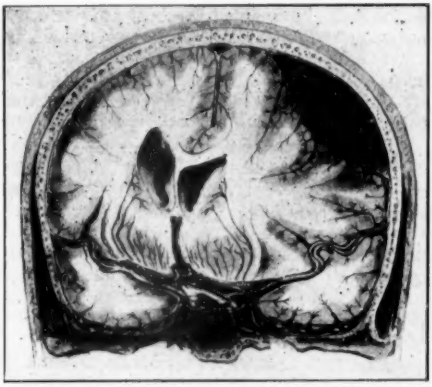


FIG. 5.—Lateral displacement of the brain, especially of the basal structures, from an increasing subdural clot, showing progressive stretching of the perforating branches of the anterior and middle cerebral arteries. (N. M. Dott. Thomson and Miles Manual of Surgery (1939) **2**, 670. London.)

callosum and laceration of the septum pellucidum by the falx indicates the severity of upward and backward rotation of the hemispheres by a posterior vertex deceleration injury, with stretching of the perforating branches of the anterior and middle cerebral arteries and infarction of their territory of supply.

Further evidence of such vascular lesions and the problems of the acceleration head injury are demonstrated in the following case history.

A man of 63 sustained a severe frontal deceleration injury. He was unconscious from the beginning and showed a left hemiparesis. There was no fracture of the skull. Because of deterioration in his level of consciousness eleven hours later a right carotid angiogram was performed. The cortex of the right hemisphere was seen to be displaced 1 cm. from the dura indicating the presence of a subdural hæmatoma.

The hæmatoma was evacuated and torn frontal lobe veins, which were the source of bleeding, were coagulated. However, he improved only temporarily, developed a complete left hemiplegia and died four days later. Autopsy showed a thrombosis of the right internal carotid and middle cerebral arteries which arose at the site of origin of the perforating branches of the middle cerebral artery. Early infarctive changes were seen in the territory of the right middle cerebral territory and in the putamen of that side. In addition there was œdema of the heads of both caudate nuclei, especially marked on the right.

This patient illustrates the several effects of severe acceleration injury, the fronto-temporal lacerations, the subdural hæmatoma arising from them, and finally stretch injury of the perforating branches of the middle cerebral artery which in this case probably induced thrombosis of the middle cerebral artery and of the internal carotid artery. No damage of the intima of the internal carotid artery was demonstrated histologically.

There is a striking similarity between the clinical behaviour, and indeed the EEG changes, of the severely head-injured and those suffering from the severe effects of rupture of an anterior communicating aneurysm. In this latter condition at autopsy ischæmic lesions in the territory of supply of the perforating branches of the anterior cerebral arteries have been demonstrated, the result of spasm following rupture of the aneurysm (Gillingham and Watson, 1953). It may well be that interference with these important perforating arteries by stretch and subsequent spasm may help to explain the prolonged disorders of consciousness and the autonomic and metabolic dysfunctions that follow severe acceleration head injury.

Similar lesions of the perforating branches of the posterior cerebral arteries have also been demonstrated in head injury but in our experience they are uncommon.

So much for the immediate pathological changes which follow the sudden cerebral displacements of acceleration injury. Of far greater practical implication are their complications, the hæmatomas and cerebral swellings, which are often remediable lesions if dealt with promptly. Although difficult to recognize in the already unconscious patient, where there has been no lucid interval, knowledge of the pathological factors involved in the gradual cerebral displacements, which are associated with these expanding lesions, clarify a somewhat confused clinical picture.

Fig. 5, for example, shows a coronal section of the brain of a patient who died of a subdural hæmatoma. There is gross lateral displacement of the brain from clot. Traction upon the perforating branches of the anterior cerebral arteries causes progressive ischæmia of the hypothalamus. In the case of a patient already recovered from concussion, these vascular traction displacement effects lead to headache and increasing drowsiness. When there has been no lucid interval, they lead to increasing restlessness with increasing inaccessibility, culminating in coma. Traction upon the lateral group of perforating vessels from the middle cerebral artery, which supplies the internal capsule, leads to an increasing contralateral hemiparesis.

In addition to lateral displacement, there is an attempt on the part of the brain to make further room for itself in its closed box. At the tentorial hiatus there occurs further displacement. To accommodate the increasing volume within the supratentorial compartment of the skull the mid-brain moves downwards, and at its lateral border, the hippocampal gyrus of the temporal lobe herniates downwards between it and the edge of the tentorium. At the same time the mid-brain is pushed across and the cerebral peduncle may be pressed against the opposite edge of the tentorium, with consequent hemiparesis on the same side as the clot. Increasing herniation of the hippocampal gyrus stretches the III cranial nerve which lies below it, with dilatation of the pupil so characteristically seen in the late stages of increased intracranial pressure from rapidly expanding unilateral supratentorial lesions.

As the mid-brain is displaced downwards, its tiny vessels of supply, which arise from the basilar artery and its short circumferential branches, become progressively stretched. The artery is held up by its posterior cerebral branches over the edges of the tentorium and by the posterior communicating arteries, and is unable to follow the downward movement of the mid-brain (Blackwood and Dott, 1952). Resulting ischæmia of the mid-brain causes further impairment of consciousness. Finally, as ischæmia progresses, decerebrate rigidity appears and, with infarction of the mid-brain, a fatal outcome soon follows (Fig. 2).

It has been our practice over the past two years, following the removal of intracranial clot, and with the head still open, to correct these displacements by the rapid and forcible injection of approximately 100 c.c. of saline into the lumbar theca. As the tentorial herniation is reduced, there is often a sudden lessening of resistance to injection and usually an immediate improvement in the condition of the patient (Alexander and Dott, 1952).

With the recognition of such displacements from clot or swelling, it can be seen that a good deal depends upon their speed of formation and this dictates the urgency for their relief.

From our present knowledge of the pathology of head injury, it is probable that the direct lesions of the cerebral substance are not fatal, and their complications, the hæmatomas and contusional swelling, with the displacements and impactions which arise from them, are all remediable lesions if dealt with promptly. Indirect forms of injury, ischæmic damage of the hypothalamus and basal brain structures from sudden stretching of their vessels during acceleration injury, are associated with disturbances of consciousness, autonomic and metabolic dysfunction. When severe, they are seldom amenable to treatment, and in our present state of knowledge, usually fatal.

The adequate care of the head-injured is dependent, therefore, upon a lively appreciation of the clinical picture which results from the sudden displacements of injury in the first instance, and the gradual displacements of its complications in the second.

I would like to express my thanks to Professor Norman Dott for his generous help with the correction of the manuscripts of this paper and for the use of the illustration in Fig. 5.

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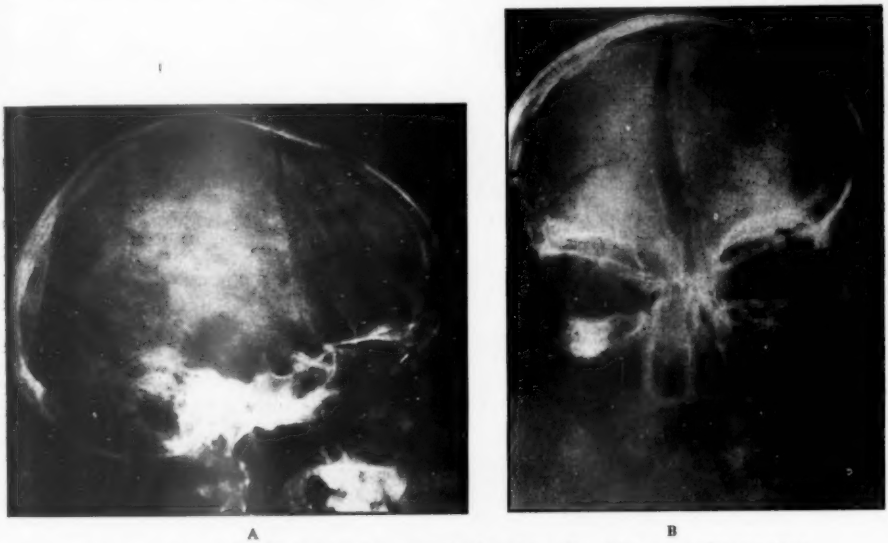
Miss Diana J. K. Beck (Neurosurgical Department, Middlesex Hospital, London):

The Operative Treatment of Head Injuries

Cerebrospinal rhinorrhœa.—Before coming to the main subject of my remarks, the traumatic intracranial hæmorrhages, I should like to say something about cerebrospinal rhinorrhœa. This may be of transient duration and so escape notice, or it may only appear as the result of ill-advised and incomplete operations on patients with a severe closed head-injury, associated with a fracture extending into the para-nasal air sinuses. This is exemplified by a child of 9½ who came under my care two and a half years ago, six weeks after her admission, unconscious, to another hospital.

X-rays showed an extensive vertical fracture into the ethmoidal region (Fig. 1, A and B). At operation



A B

FIG. 1.—A, X-ray of skull showing fracture extending into ethmoidal region (lateral view). B, A.P. view of same.

that night blood clot and brain were found extruding through the fracture line. Loose bone fragments were removed and the coronal wound closed. Next day, cerebrospinal fluid was escaping from both nostrils. Her course after operation was unsatisfactory and she steadily deteriorated. Six weeks after the accident she was emaciated, excitable, restless, irritable, doubly incontinent and grossly demented. Speech was restricted to expletives.

Except for a right hemianopia, abnormal neurological signs were insignificant. She had bed-sores and severe contracture deformities of the lower limbs, in which there were no spontaneous movements (Fig. 2).

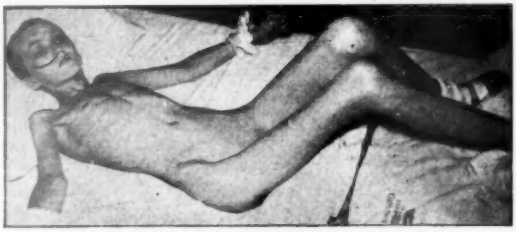


FIG. 2.—Patient six weeks after accident.

X-rays of the skull showed large bilateral frontal aerocœles and a spontaneous ventriculogram (Fig. 3). She was fit for operation ten days after admission, i.e. nearly eight weeks after the accident. Cortex, 1 mm. thick, was found enclosing large collections of air in the frontal lobes, and when

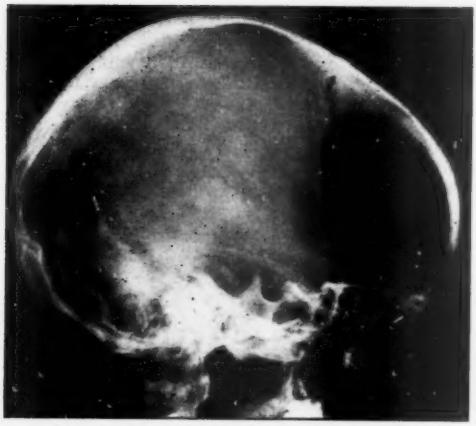


FIG. 3.—Frontal aeroceles and spontaneous ventriculogram.

FIG. 4.—Showing empty anterior cranial fossæ at end of operation.

these and disintegrated brain were removed, it appeared that there was no brain tissue in the anterior cranial fossa (Fig. 4). Dural tears extending to both ethmoidal regions and overlying the fractures were repaired with fascia lata.

Two and a half weeks later she was up playing with toys, feeding herself and recognizing pictures of well-known public figures. She is now at a school for the physically handicapped, superficially alert, good-tempered in her home, able to read well but without ability to retain for long the content (Fig. 5). She will eventually need institutional care for she is in some ways like an individual who has had a bilateral frontal lobectomy.

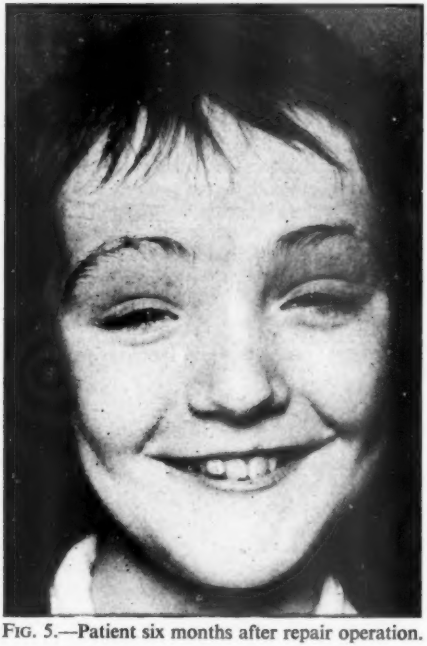


FIG. 5.—Patient six months after repair operation.

Traumatic intracranial hæmorrhages.—These may be extradural, subdural or intracerebral. It is a sobering thought that forty years after Trotter's (1914–15) beautiful description of subdural

hæmorrhages, the death-rate from extradural hæmorrhage should still be 50% and that from subdural hæmorrhage 60%. Lewin (1949) and James and Turner (1951) have all recently drawn attention to this sorry state of affairs. I do not know the figures for intracerebral hæmorrhages due to trauma, but I am sure that all need not die.

In many patients there are hæmorrhages at more than one of these sites: shock and injuries elsewhere may make their recognition extremely difficult.

The classical picture of extradural hæmorrhage has perhaps made too deep an impression on the minds of surgeons for, whilst rapidly developing coma following the lucid interval that succeeds transient loss of consciousness is common in these cases, in many the clarity of the picture is blurred by coincident injury to the brain or elsewhere.

I have had several cases of extradural hæmorrhage in children. One, a child of 5, showed the classical clinical picture of concussion, lucid interval and coma. After a 15-foot fall she was dazed for a few seconds: her unaccustomed quietness caused her father to bring the child up to London. During the hour's journey by ambulance she developed a right hemiplegia and became completely unconscious. On arrival at the Middlesex Hospital she was comatose: she had widely dilated and inactive pupils and absent corneal reflexes. She had a complete right hemiplegia. There was a soft diffuse swelling in the left temporal region—a very important sign.

A large left extradural clot was immediately evacuated under local anæsthesia. Bleeding was from veins emptying into the superior longitudinal sinus and its escape through a wide fracture had acted as a safety valve. She talked normally and moved her right limbs whilst still on the operating table.

Extradural hæmorrhage may be of such extreme urgency that every surgeon in the country must know how to deal with it.

It is customary to divide subdural hæmatomata into acute and chronic varieties and this is sound, for their ætiology, development and treatment are so different.

The acute variety is usually associated with a fracture and with more or less extensive brain laceration. Most of the patients are unconscious from the time of the accident. The clinical picture is one of rapidly increasing intracranial pressure, with inconstant neurological signs over the first twenty-four hours. Restlessness and increasing drowsiness should arouse suspicions and are reasons for immediate operation, if there are any localizing signs. Coma after a period of variable lucidity is a definite indication for operation. As is obvious, it is impossible to distinguish some of these cases from those of extradural hæmorrhage.

In chronic subdural hæmatoma there may be a history of momentary dazing after a blow, often so mild as to be forgotten, on the front or back of the head either in the home, at work or at play. The symptoms vary greatly and may fluctuate widely. In general they are those of raised intracranial pressure: headache is variable, drowsiness is conspicuous but it is to be emphasized that the patient may become completely alert and as quickly relapse again into coma. Mental confusion is very important as are personality changes. In some there is mild and often transitory weakness of limbs.

A building contractor aged 60 years had for six months felt very tired. Five days before admission he became unsteady in movement, showed fluctuating aphasia and confusion, was incontinent on one occasion, and for two days exhibited fluctuating drowsiness. He was regarded as having a malignant intracranial tumour: he had a moderately severe aphasia, a moderate right hemiplegia and mild papillœdema. After arteriography, hemiplegia became complete: he had a right hemianopia and speech was limited to "No". The arteriograms showed unequivocal evidence of a large left subdural hæmatoma. A solid clot bounded by a thick membrane was found on making the usual burr-holes and the need to turn an osteoplastic flap for its removal seven days later was expected.

Sometimes these cases of chronic subdural hæmatoma become a matter of great urgency.

A Polish kitchen-porter, aged 35, was admitted drunk on New Year's Eve, 1948. He had a small left temporal stab wound. Mild right-sided signs disappeared in four days. There was a history of dragging the right leg for two months. When he was readmitted three weeks later with headache, drowsiness, confusion and weakness of the left arm, he was found to have a strongly positive Wassermann reaction. Whilst under investigation he became suddenly extremely ill: when I was called in he was comatose, had Cheyne-Stokes respiration and inactive and widely dilated pupils. The left limbs were paralysed and flaccid, the right spastic.

The evacuation of a large left subdural hæmatoma through burr-holes resulted in recovery of consciousness and power on the table.

The necessary operative procedure is to make bilateral parietal and frontal burr-holes in the first place: these must be bilateral because the hæmatomata are often and unexpectedly found on both sides and because, as in the case just cited, the hæmatoma may be on the side other than that suggested by the clinical findings.

The association of subdural hæmatoma with an intracerebral clot is well illustrated by the case of an Irish bar-tender, aged 35 years (Beck, 1953). He had been discharged from the Royal Navy in 1944 as he was said to be psychotic and because he had a high blood pressure. A pugnacious man, he had collapsed going home one night: in spite of an amnesic period of some hours he insisted on going to work next day—when he again collapsed. On admission to the Middlesex Hospital he

was febrile, conscious, but grossly confused, with slurred speech. He had a stiff neck, a moderate right hemiplegia and bilateral plantar extensor reflexes. He was incontinent and his cerebrospinal fluid was bloody. His blood Wassermann reaction was positive. He was a very ill-looking cyanosed man whose attention was difficult to hold. He had bilateral papilloedema of two dioptrics and apraxia of a moderately weak right arm.

Arteriography suggested that both an intracerebral and subdural hæmatoma were present. At operation a solid subdural clot 3 cm. thick was removed from the left fronto-temporal-parietal region and then the frontal intracerebral clot was seen emerging from a ragged tear in the left inferior frontal gyrus: this clot was removed from a cavity measuring $5 \times 4 \times 3$ cm.

He made an interrupted recovery and was walking five miles two months later. He has been readmitted on two subsequent occasions in status epilepticus after drinking bouts.

An intracerebral clot may occur as the result of trauma, or may be the cause of an accident. A woman of 60 years fell down some church steps and was found almost unconscious and smelling of alcohol. On admission to the Middlesex Hospital her left pupil was larger than the right and she was stuporous, restless and incontinent. During the next two weeks she was confused but there were no localizing neurological signs. Then she developed expressive and receptive aphasia, together with right-sided neurological signs. X-rays had revealed no fracture, but arteriography demonstrated a space-occupying lesion in the left temporal lobe, which proved at operation to be a solid intracerebral clot. She never at any time had a raised blood pressure and made a complete recovery.

The traumatic hæmorrhages within the skull are of immense importance because so many occur after the patient has recovered from the early effects of a head-injury; these patients should not die. They do so in their homes and in hospital and we take what comfort we can when the pathologist tells us that there were small brain-stem hæmorrhages. These may well be the late result of tentorial herniation in the presence of a blood clot that we should have removed. There is no room for complacency in any of us, for neurosurgeons miss these lesions too—and we can best diminish the death-rate from this cause by careful examination and re-examination of the patient and prompt and appropriate surgery.

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Mr. John Bruce mentioned the advantage to the general surgeon of a neurosurgical "Flying Squad" whose services were valuable in cases of severe head injury. He asked for guidance on the time and the value of radiological examination in head injuries. **Mr. D. L. B. Farley,** pointing out some of the dangers of lumbar puncture in head injury, asked for guidance regarding its general use. **Professor C. G. Rob** described a method of nasal tube feeding by a liquefied normal diet which was of value in the unconscious patient. He also raised the question of the danger of precipitating thrombosis by arteriography in the presence of possible damaged arteries. **Mr. D. H. Patey** raised the question of dealing with the acute type of extradural hæmatoma which might be fatal in a few hours.

In reply, **Mr. Lewin** described briefly the method of teaching the management of head injuries at Oxford where all students worked in the Accident Unit for six weeks. On the question of the very acute extradural hæmatoma, he stated that the problem was capable of being dealt with in three ways—efficient ambulance transfer arrangements, neurosurgical "Flying Squads", or emergency operation by the general surgeon, depending on individual circumstances. He mentioned three points in management:

(1) Deterioration in the condition of a patient with head injuries, who has up till then been improving, means a complication.

(2) X-rays should be taken on admission, if possible, provided the patient is not shocked and not restless.

(3) Lumbar puncture should not be done in the acute stage if there is any suspicion of cerebral compression.

Mr. Gillingham described some of the ways in which the subject of head injuries was taught in Edinburgh. Apart from the "Flying Squads", they had introduced in Scotland, where geographic conditions were complex, the system of telephonic communication between the neurosurgeon and a general surgeon who had a case of head injury about which he was worried. In reply to Professor Rob, he said that the advantages of arteriography outweighed its dangers.

Miss Beck also emphasized the importance of sound student training. She was opposed to the routine intravenous injection of hypertonic saline, and felt that this procedure should always be controlled by pressure reading.

Clinical Section

President—JAMES L. LIVINGSTONE, M.D., F.R.C.P.

[*May* 14, 1954]

MEETING AT THE LUTON AND DUNSTABLE HOSPITAL, LUTON, BEDS

Aspergillosis Complicating Pulmonary Tuberculosis.—DONALD BARLOW, M.S., F.R.C.S.

M. N., female, aged 25. Had bronchiectasis of the whole left lung with a large apical cavity and secondary tuberculous infection. A left pneumonectomy was undertaken and during the removal of the lung the apical cavity was opened.

Aspergillosis developed in the pleura and later she had a bronchopleural fistula. She became sensitized to the fungus and ran a persistent high temperature and steadily became more ill and emaciated. The fungus infection in the pleura failed to respond to any of the known antibiotics, to PAS, isoniazid or the sulphonamides. It was resistant to iodides, neoarsphenamine, actidione and hydroxystilbamide. Fortunately it responded well to Phenoxetol and after prolonged treatment of the pleural cavity with this drug, she eventually made steady improvement and has now put on 1½ st. in weight. During her illness the ribs on the left side became osteomyelitic but have now regenerated. After many weeks in hospital the pleural cavity became negative for both tubercle and the fungus, but recently both have been positive again.

The treatment of such a case is very difficult. It is felt that she should have a thoracoplasty to reduce as far as possible the size of the cavity and the area for toxic absorption and eventually she may have to have a pleurectomy with mechanical closure of the fistula.

The aspergillus was first described by Micheli in 1729; when it infects the human subject it tends to produce the following symptoms: (1) Hæmoptysis. (2) Cough with sputum. (3) Prolonged pyrexial attacks. (4) Asthmatic attacks.

X-rays of patients with hæmoptysis, cough and sputum, tend to present a fairly characteristic appearance, namely, a cavity in which there is a semi-solid mass presenting a crescentic air shadow on one side of it.

In retrospect, the bronchograms of our patient show a mass (aspergilloma) with an air-space round it in the large left apical cavity. Some patients may present merely with bronchiectasis and these may have asthmatic attacks due to masses of the fungus in the bronchi. The fungus is often coughed out of one collapsed lobe only to produce a similar lesion in another and radiographs show changing areas of lobular or lobar collapse. The sputum contains tiny brownish granules composed of the mycelium with Charcot-Leyden crystals and Curschmann's spirals. The blood usually shows a fairly marked eosinophilia and on bronchoscopy one can sometimes see masses of fungus in the bronchi or a polypoid mass of granulation tissue.

The commonest of the four types of aspergillosis is that caused by *Aspergillus fumigatus*.

Dr. **Neville Oswald** felt that Mr. Barlow's statement that aspergillosis usually occurs within chronic cavities in the lungs was rather sweeping, as it was liable to occur as a terminal complication in cachectic states without any pulmonary cavitation. Also, of course, it was a well-recognized condition in pigeon fanciers who were in the habit of feeding their birds from their own mouths. Mr. Barlow's patient obviously would require a thoracoplasty at some time, but the present combination of infection by tuberculosis and aspergillosis in addition to the rather recent osteomyelitis of the ribs, made the operation rather hazardous at this stage.

Myocardial Sarcoidosis.—D. R. RYRIE, M.B. (for T. PARKINSON, M.D.).

M. W. L., aged 23. Press operator.

History.—January 1954; Patient was referred to Luton Chest Clinic because of loss of weight over the last year. X-ray showed enlargement of hilar lymph nodes. On 12.12.53 the Mantoux reaction was negative to 1/100. A marked pulse irregularity was noted and the patient was referred here by Dr. A. B. Shaw with a tentative diagnosis of sarcoidosis with myocardial involvement.

25.1.54: Admitted for investigation. Physical examination showed only a markedly irregular pulse, clinically resembling that of auricular fibrillation. There were no enlarged lymph nodes, no eye signs and no enlargement of the liver or spleen.

Over.

Investigations.—Chest X-ray (Fig. 1): Hilar lymph-node enlargement. X-ray hands and feet normal. ECG (Fig. 2): Partial A-V block with Wenckebach's phenomenon. Mantoux reaction strongly positive to 1/100. E.S.R.: 3 mm. in one hour (Westergren), Hb 110%. W.B.C. 8 600. Plasma proteins: albumin 5·2 grammes%, globulin 1·8 grammes%. Serum calcium 10·2 mg.%. Antistreptolysin titre 180 units/c.c. Liver biopsy (Fig. 3): Serial sections showed one epithelioid tubercle with a definite area of central necrosis.

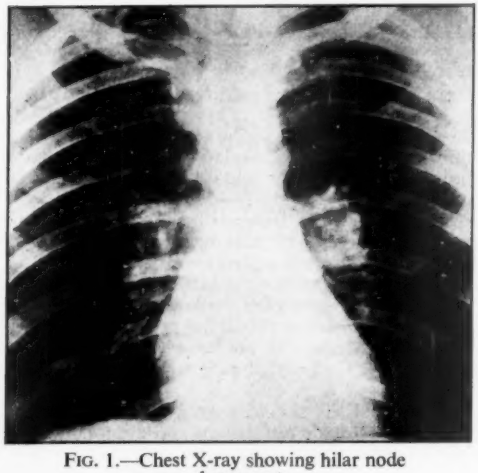

FIG. 1.—Chest X-ray showing hilar node enlargement.

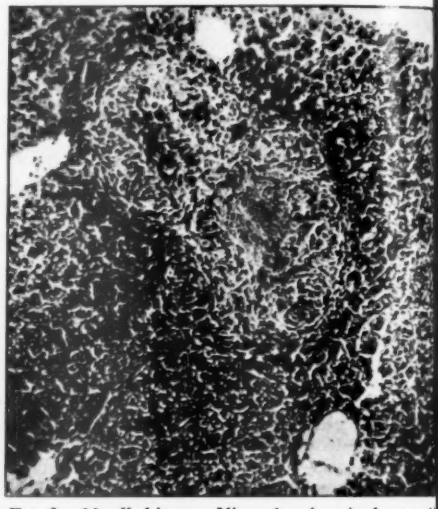

FIG. 3.—Needle biopsy of liver showing single sarcoid nodule with central necrosis. × 125.

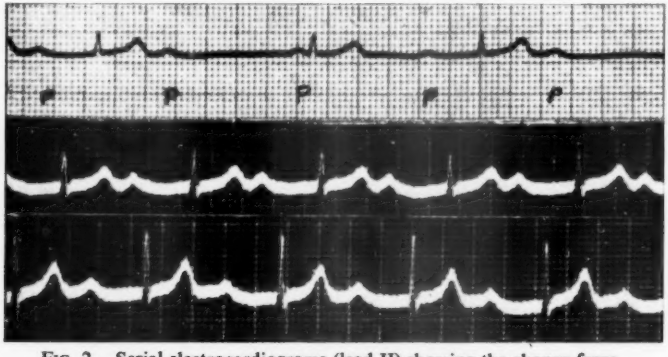

FIG. 2.—Serial electrocardiograms (lead II) showing the change from periodic A-V block to fixed prolonged P-R interval.

Comment.—The characteristic radiological lymph node enlargement and the positive liver biopsy make it virtually certain that the partial A-V block is due to sarcoidosis of the myocardium. It is of particular interest that the sarcoid nodule in the liver showed some central necrosis at the time that Mantoux conversion had just taken place. It might therefore be argued that this is a case of miliary tuberculosis and not sarcoidosis. It is known that myocardial sarcoidosis often has a fatal outcome; in many of the reported cases sudden death occurred without previous symptoms. It was thus considered essential to treat the patient immediately. Cortisone, streptomycin and isoniazid were used in combination. The results have been difficult to assess. The partial A-V block has changed from a persistent Wenckebach's type to a fixed type with prolonged P–R interval and only occasional dropped beats. There has been a gradual diminution in the size of the hilar glands on radiography. It is difficult to believe that much less would have been achieved by leaving the patient at rest in bed without specific treatment.

Sarcoidosis with Obstructive Jaundice.—D. R. RYRIE, M.B. (for T. PARKINSON. M.D.).

Mrs. L. N., aged 52. A housekeeper.

History.—Admitted to hospital 30.10.53. She had been off colour for some months with vague indigestion and a distaste for food. Six weeks before admission she had become jaundiced and remained so until admission.

On examination.—Jaundiced. Scratch marks on skin. Liver palpable 3 fingerbreadths. Gall-bladder also palpable. Stools pale. Urine contained bile.

Investigation.—Liver function tests: Alkaline phosphatase 35 K.A. untis. Van den Bergh 12 mg. bilirubin%. Thymol turbidity 1 unit. Paul-Bunnell negative. Liver biopsy: appearances of obstructive jaundice only. Plasma proteins: albumin = 4·8 grammes%, globulin = 1·7 grammes%. E.S.R. 58 mm. in one hour (Westergren). X-ray chest: Mediastinal lymphadenopathy. X-rays of bones: normal. Mantoux reaction negative 1/100. Serum calcium 9·6 mg.%.

Operation 1.12.54 (Mr. D. Tooms).—Large tense gall-bladder. Hard mass palpable in head of pancreas. Enlarged lymph nodes in porta hepatis and along splenic vessels. A gland was taken for biopsy and a cholecystoduodenostomy was carried out.

Biopsy report of gland.—Sarcoidosis (Fig. 1).

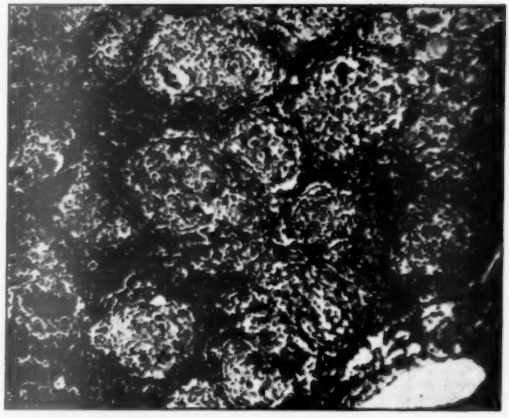

FIG. 1.—Section of abdominal lymph node showing sarcoid nodules. × 80.

Post-operatively the patient improved and the jaundice decreased.

27.1.54: Readmitted from convalescent home with severe upper abdominal pain and fever. The urine was loaded with sugar and ketones. The liver was bigger than previously.

Investigations.—Blood sugar (three hours after meal) 278 mg.%. Repeat liver biopsy: No evidence of sarcoidosis. Plasma alkaline phosphatase 51 K.A. units. W.B.C. 8,000.

Comment.—This case was condidered pre-operatively to be a case of reticulosis with obstructive jaundice. At operation the pancreas was found to be so hard that it was thought to be neoplastic. Biopsy of a near-by gland, however, showed characteristic changes of sarcoidosis. A month after operation the patient developed acute diabetes and it was thought that this was sufficient to make a diagnosis of pancreatic sarcoidosis. Unfortunately, amylase tests and duodenal intubation were not done in the acute phase. In view of the progressive nature of the disease, treatment with cortisone, streptomycin and isoniazid was given. Approximately 30 units of insulin were required daily to control the diabetes. There has been a slow clinical recovery with diminution of liver size, disappearance of jaundice and regression of mediastinal lymphadenopathy.

Sarcoidosis of the pancreas must be extremely rare but it has been reported on a few occasions: there are no recorded cases in which it was accompanied by acute diabetes.

Dr. Neville Oswald thought that the prognosis in this patient with obstructive jaundice was poor, because she had the chronic type of sarcoidosis associated with middle age.

Carcinoma of the Bronchus.—J. BRIAN SHAW, M.D., and M. A. EROOGA, M.B.

B. ., male, aged 34, aircraft fitter, was referred to Luton Chest Clinic for a miniature film. Because of abnormal shadowing in the left mid-zone the patient was recalled. He gave a history of having had pain in the left submammary region two weeks previously. At first it was pleural in type but was later described as a bruised feeling. A slight temperature at the onset of illness responded to Sulpha-

mezathine given by his own doctor. A cough which he had for several years did not alter in character; there was no sputum and he complained of no other symptoms apart from tiredness which was attributed to overwork (sixteen hours a day).

Family and past medical history were non-contributory. A mass miniature X-ray taken in February 1952 was re-scrutinized and showed no abnormality. He smokes fifteen cigarettes a day.

On examination, the only abnormality noted was some crepitations below the left scapula. A chest radiograph showed on the anteroposterior view a small area of abnormal shadowing in the second right interspace and an abnormal shadow in the left lower zone with an indefinite round opacity close to the hilum (Fig. 1).

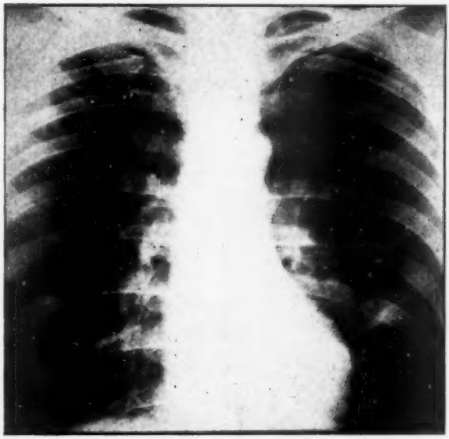

FIG. 1.—Large film showing aspiration pneumonia in second right interspace and in lingular segment left lower lobe.

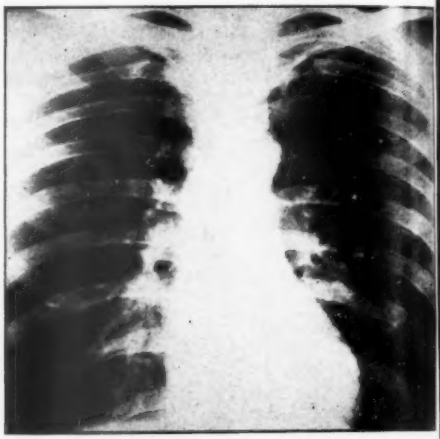

FIG. 2.—Radiograph one month later showing clearing of aspiration pneumonia and persistence of shadow just below left hilum.

A left lateral view confirmed that there was a lesion in the lingular segment of the left upper lobe. E.S.R. was 30 mm. in the first hour (Westergren). Laryngeal swabs were negative on culture for tubercle bacilli.

The patient returned to work and was seen again a month later when he still complained of some slight and occasional pain on the left side of his chest. Chest X-rays showed the right lung to be normal and clearing of the shadow close to the hilum on the left side. The rounded opacity noted

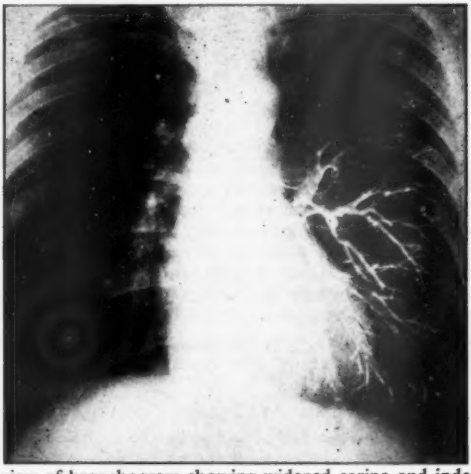

FIG. 3.—P.A. view of bronchogram showing widened carina and indentation of one of the inferior branches of lingula.

above still persisted (Fig. 2). A lateral view and fluoroscopy confirmed that this was lying anterior to the main hilar shadows. Blood count: W.B.C. 8,800 (neutros. 60%, lymphos. 30%, monos. 4%, eosinos. 6%). E.S.R. 2 mm. in the first hour (Westergren).

Left bronchogram using Dianosil in oil mixed with sulphanilamide showed: (1) Widening of the carina between the main branches of the lingular bronchus. (2) Indentation of one of the inferior branches of the lingular bronchus by a rounded mass. (3) Filling of the bronchi beyond the indentation was incomplete but the bronchi appeared to be slightly widened (Fig. 3).

Tomography.—Serial exposures while the bronchi remained filled with opaque material further demonstrated the widened carina between the superior and inferior branches of the lingular bronchus due to a round mass. Indentation of an inferior branch bronchus was confirmed and a stump of an obstructed bronchus leading into the centre of the mass was revealed (Figs. 4 and 5).

FIG. 4.—Tomogram showing stump-like appearance of one of the inferior lingular branch bronchi blocked by the bronchial carcinoma.

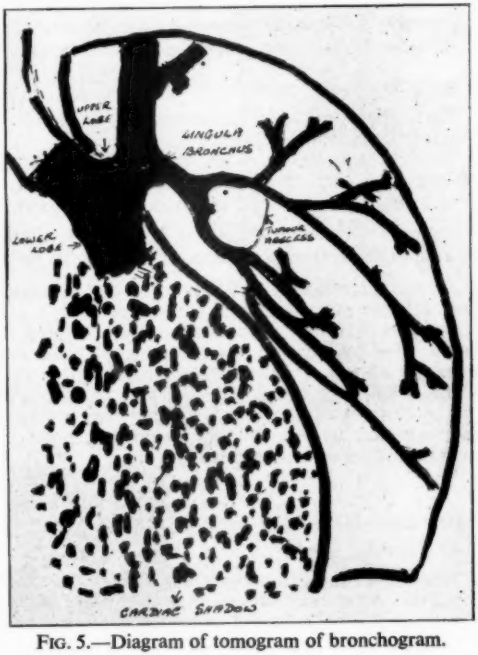

FIG. 5.—Diagram of tomogram of bronchogram.

The patient was admitted to the Thoracic Surgical Unit, St. Charles' Hospital, W.10, under the care of Mr. G. C. W. James, F.R.C.S.

Investigations.—Chest X-ray showed no change. Sputum: No malignant cells seen. On culture numerous *Strep. viridans* grown.

Operation report.—Lung free, large emphysematous bullæ noted at apex. It was not possible to strip the lingula, and at this stage the mass broke to reveal a cavity full of pus and it was decided to take the anterior segment of the upper lobe as well. The lung then stripped out fairly easily leaving a minimal air leak from raw surface. Routine closure.

Histology report.—Solid trabecular squamous carcinoma infiltrating wall of the bronchus. Glands and vessels in the vicinity were unaffected. The section of the specimen removed showed that the rounded mass was in fact an abscess formed by the breaking down of the carcinoma.

The patient was discharged in February 1954, seven weeks after his original X-ray and has remained well to date.

Comment.—This case demonstrates a carcinoma of the bronchus presenting as a bilateral aspiration type of pneumonia with transient febrile illness in a young man of 34 years. It illustrates the aid in reaching a correct diagnosis and localization of a tumour beyond the view of a bronchoscope by the combination of tomography and bronchography. The bronchogram indicated an expanding intrapulmonary lesion and failed to show an obstructed branch bronchus. The tomogram of the bronchogram, however, clearly demonstrated the stump of a bronchus obstructed by the growth.

Sarcoma of the Uterus (Two Cases).—J. W. S. HARRIS, M.B., M.R.C.O.G. (for G. C. BRENTNALL, M.D., M.R.C.O.G.).

I.—P. T., aged 34.

Normal pregnancy 1944. Incomplete abortion 1948. Third pregnancy 1952. Lower abdominal pain in early months—fundal fibroid noted. Spontaneous full-term delivery, 16.8.53. Post-natal examination October 1953: Uterus the size of a 14 weeks' pregnancy, no symptoms. January 1954, admitted for myomectomy—slight menorrhagia, uterus the size of a 16 weeks' pregnancy. 20.1.54: Laparotomy: Nodular mass of growth over anterior surface of uterus. Total hysterectomy and bilateral salpingo-oophorectomy. Enlargement of pelvic and para-aortic lymph nodes. Chest X-ray normal.

Histological report.—Sarcoma of low-grade malignancy. No evidence of stromatous endometriosis.

February 1954: Full course of deep X-ray therapy.

At present, no evidence of pulmonary metastases and patient well.

II.—F. G., aged 40.

Early abortion 1941. Second pregnancy 1952. Fundal fibroid noted at third month. 6.12.52: Delivered. Menorrhagia after delivery.

24.3.53: Myomectomy—one large fibroid which appeared normal and several seedlings removed. Histologically, sarcomatous change present in the two fibroids. Chest X-rays normal. 6.5.53: Total hysterectomy and bilateral salpingo-oophorectomy. No microscopic malignant tissue found.

Progress.—Secondary deposits in pelvis July 1953. Deep X-ray therapy without lasting effect. Pulmonary metastasis February 1954. Died April 1954.

Discussion.—Sarcoma of the uterus is uncommon. Three cases have been seen in the Luton and Dunstable Hospital in the past three years.

It seems that the hormonal stimulation of pregnancy may have been an ætiological factor in these cases. The relationship between pregnancy and the onset of sarcomatous change in uterine fibroids does not appear to have received comment in recent literature. There is no distinctive symptom complex and diagnosis at operation may not be possible owing to the benign appearance of the fibroids.

These two cases seem to indicate that pregnant women with fibroids should be followed up at frequent intervals after delivery and that the postponement of myomectomy until breast feeding is discontinued may lead to unwarranted delay.

Cystinosis.—GRAHAME FAGG, M.D.

M. H., male, aged 6.

History.—The birth weight was 8 lb. 4 oz. Operation for pyloric stenosis was performed at 3 months. After this he developed normally up to the age of a year. Thereafter, although he continued to gain slowly he developed severe thirst, anorexia and polyuria. He was first seen aged 3½ years when his weight was 24½ lb. (average 35 lb.) and his height was 33 in. (average 38 in.). He was uræmic (blood urea 94 mg.%), there was a trace of albumin in the urine, the alkali reserve was 30·9 vol. CO_2% and I.V.P. was unsuccessful owing to poor concentration of dye.

In the family there are three other siblings. Two had symptoms similar to the patient and died of acute dehydration and collapse with measles at the ages of 3½ and 2¼ years respectively. Autopsy showed cystine storage throughout the tissues in both cases. The third sibling is aged 15 months and so far is well. The parents are apparently normal and unrelated, and there is no history of similar cases on either side of the family.

The child was considered at that time to be a case of renal acidosis and treatment with alkalis and extra fluids resulted in 3 lb. gain in weight in six weeks. Amino-acid chromatography was said to be normal.

During the next year he made poor progress and was readmitted when 4¾ years old. At this time his height was still 33 in., and weight 24½ lb.; bone X-ray showed no definite evidence of rickets (Fig. 1). The blood urea ranged between 280 mg.% and 86 mg.%, improving when he was well hydrated. The alkali reserve rose to 76 vol. CO_2% with the administration of alkalis. Blood chlorides and blood calcium were normal. The urine had traces of albumin and sugar and could be concentrated to a specific gravity of 1016 by withholding fluids overnight.

After the death of the two siblings further amino-acid paper chromatography studies were done on the patient and his parents. The results for the patient are as follows: (1) Negative, (2) "Amino-aciduria with proline, leucine, valine, phenylalanine and tyrosine excreted in very marked excess over the normal; alanine, cystine and lysine are less markedly excessive. This is a typical renal failure pattern, the presence of cystine being fully consistent with cystinosis. Cystinuria (of the classical, stone forming, cystine-lysine-arginine type) can be excluded by this amino-acid pattern.

"Sugars present: Glucose about 25 mg.% (normal up to 10 mg.% but rarely over 5 mg.%). This urine is, however, so dilute that this glucose excretion must be regarded as grossly excessive and fully consistent with a diagnosis of cystinosis."

Both parents were negative.

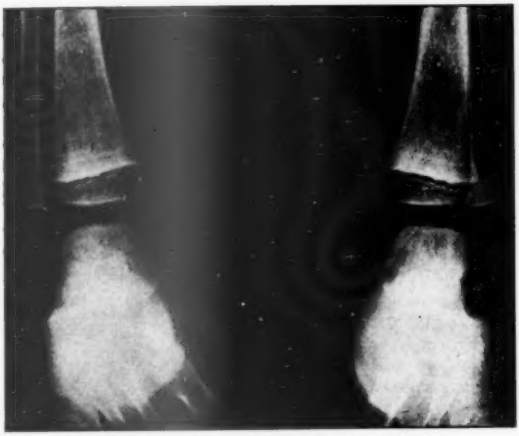

FIG. 1.—X-ray, September 1952. No definite evidence of rickets.

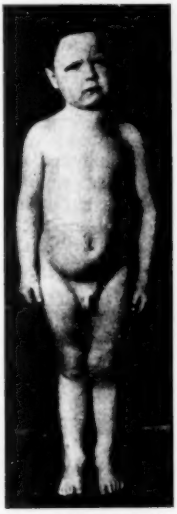

FIG. 2.—M. H., aged 6½ years.

Present condition.—The height is 36 in. (normal for age 45 in.) and weight 29 lb. (normal for age 47 lb.) (Fig. 2). He has marked X-ray evidence of rickets (Fig. 3) and cystine deposits are visible in the corneæ when viewed with a lens.

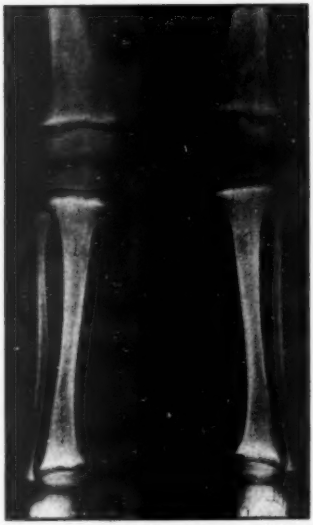

FIG. 3.—X-ray, May 1954. Gross rachitic changes.

Biochemistry results: Blood urea 114 mg.%; serum phosphorus (inorganic phosphates) 3·0 mg.%; serum calcium 8·5 mg.%; serum chlorides 610 mg.%; alkali reserve 37·6 vol. CO_2%.

He is being treated with alkalis and large doses of vitamin D in an attempt to cure the rickets.

Hydrocalicosis.—HENRY CLARKE, F.R.C.S.

H. F. A., male, aged 36. Welder.

History.—First seen 21.3.50. Attacks of dragging pain left side of abdomen on exercise, radiates to groin not to back. Frequency—Day/Night = two-hourly/0.

On examination.—No abnormality detected.

Investigations.—Mid-stream urine; no abnormal deposit. Culture: small growth of coliform bacilli, probably contaminants. I.V.P.: ? intrarenal cavities right. Cystoscopy and right retrograde pyelogram: hydrocalicosis right. Three early morning specimens of urine—no acid-fast bacilli, few leucocytes.

Progress.—As the patient had no symptoms referable to the right renal tract it was decided to observe him. When examined by a right retrograde pyelogram on 16.5.52, 20.2.53, and 9.4.54, on each occasion there was slight increase in the hydrocalicosis, although the patient still had no symptoms referable to the right renal tract.

On one occasion (20.2.53) he complained of pain in the right back which at first was thought to be due to his kidney but was later proved to be only fibrositis and soon responded to physiotherapy.

Comment.—This case of hydrocalicosis, or calyceal diverticulum as it is better called (Prather, 1941), was discovered accidentally during a urological investigation. The latter was done because the patient complained of pain in the left iliac fossa and frequency. However, unlike some of the reported cases (Mathieson, 1953) the cysts have steadily increased in size over the last four years (Figs. 1 and 2) but the patient still has no symptoms referrable to the right urinary tract. Moore (1950) considered that the condition was due to achalasia of the calyceal sphincters and the fact that this patient's cysts have greatly increased in size would tend to suggest that there was an obstructive element and might tend to support this theory or the ideas of Hyams and Kenyon (1941) who considered that it might be due to an obliterative pyelonephritis producing a stricture at the neck of the calyx. However, the cases reported by the latter authors showed much grosser changes than with this present case. Other authors (Mathieson, 1953) consider these cysts to be congenital. It is obvious that further investigation of this condition is required. The theories held at present do not completely explain it and there appears to be considerable confusion about terminology.

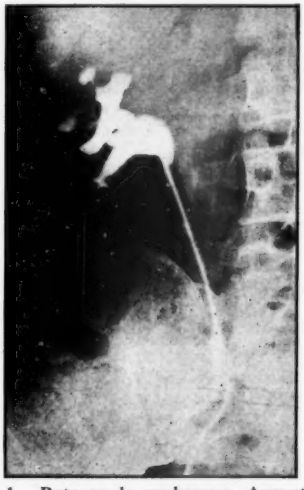

FIG. 1.—Retrograde pyelogram, August 1950, showing state of calyceal diverticulum when originally discovered.

FIG. 2.—Retrograde pyelogram, April 1954, showing definite increase in size over the last four years.

The condition is not as uncommon as one would expect from reading the literature but it so rarely gives rise to symptoms until some complication, such as recurrent infection or the formation of calculi, draws attention to it. In this particular case, I feel that no treatment is indicated at the moment.

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Section of Endocrinology

President—RAYMOND GREENE, M.A., D.M., F.R.C.P.

[*March* 24, 1954]

DISCUSSION ON HYPOTHYROIDISM

Dr. Oliver Garrod and Dr. I. C. Gilliland (Post-Graduate Medical School of London):

The Assessment of Endocrine Function in Primary and Hypopituitary Myxœdema

Means *et al.* (1940) drew attention to the severe myxœdema that may occur in the course of anterior pituitary failure. Many subsequent authors (including Statland and Lerman, 1950; Querido and Stanbury, 1950; Despopoulos and Perloff, 1950) have stressed the difficulty there may be in distinguishing hypopituitary myxœdema[1] from primary hypothyroidism. A correct diagnosis can usually be made by careful assessment of the history and physical findings. There is, however, a small group of cases in which the cause of the myxœdema can only be decided after special investigation or prolonged observation.

Because an isolated failure of thyrotrophic hormone (T.S.H.) secretion has not yet been shown to occur in man, the problem theoretically should be simple. Is the myxœdema, common to both conditions, due to a primary failure of the thyroid gland, or is it part of a secondary failure of all the glands whose function is maintained by pituitary trophic hormones? Thus, the presence in large or normal amounts of pituitary trophic hormones such as follicle-stimulating hormone (F.S.H.) or T.S.H. should exonerate the pituitary gland; alternatively, the finding of normal adrenal and gonadal function in a patient with myxœdema might indicate that pituitary function is adequate. Unfortunately, severe hypothyroidism *per se* can cause profound metabolic effects in all the body tissues, including the pituitary and other glands; and these effects, if prolonged, may lead to more widespread endocrine failure. For example, patients with severe myxœdema may have a loss of axillary and pubic hair, amenorrhœa or impotence, very low 17-ketosteroid excretion and hypoglycæmic unresponsiveness; and adrenal response to ACTH may be defective in primary myxœdema (Hill *et al.*, 1950).

In trying to establish criteria for separating these two conditions, we have assessed certain endocrine functions in 35 patients with the following clinical diagnoses:

(1) Primary myxœdema, 21 cases. (2) Hypopituitarism, 11 cases. (3) Myxœdema, of which the cause, at first uncertain, became clear only after full investigation, 3 cases (final diagnosis: 2, hypopituitarism; 1, primary myxœdema).

All of the 13 patients with hypopituitarism gave evidence of gonadal failure, and 9 had clinically obvious myxœdema. 8 gave a history of post-partum hæmorrhage, 3 were found to have pituitary tumours, and in 2 the ætiology was obscure. Of the 22 patients with primary myxœdema, this was apparently idiopathic in 18, and followed surgery or radio-iodine therapy in 4. 8 were studied more fully.

Clinical assessment of endocrine function was supported whenever possible by the following investigations:

(1) *Gonadal function*
- (*a*) 17-ketosteroid excretion (male)
- (*b*) Urinary F.S.H. excretion

(2) *Adrenal function*
- (*a*) 17-ketosteroid excretion
- (*b*) Water diuresis test
- (*c*) Insulin tolerance test
- (*d*) Electrocardiogram
- (*e*) Plasma 17-hydroxycorticosteroid concentration

(3) *Thyroid function*
- (*a*) Basal metabolic rate
- (*b*) Radio-iodine tests before and after administration of thyrotrophin
- (*c*) Plasma cholesterol concentration
- (*d*) Electrocardiogram
- (*e*) Blood thyrotrophic hormone assay

[1] We feel that this term is preferable to "pituitary myxœdema", which suggests myxœdematous involvement of the pituitary gland.

Our findings in the two groups of patients and our conclusions concerning the diagnostic significance of these tests can be summarized as follows:

(1) *Gonadotrophic Function*

Follicle-stimulating hormone (F.S.H.), as measured by the mouse uterus units contained in a twenty-four-hour specimen of urine, is probably the simplest and most reliable of the pituitary trophic hormone assays (Klinefelter *et al.*, 1943; Gorbman, 1945). A high level of F.S.H. excretion is incompatible with a diagnosis of pituitary failure. Because the majority of myxœdematous patients are of post-menopausal age, high levels are to be expected and, if confirmed, are therefore of diagnostic value in excluding hypopituitarism. On the other hand, low levels are sometimes found in severe primary myxœdema of post-menopausal age as well as in hypopituitarism, and are of much less diagnostic value. If these return to normal after thyroid treatment, pituitary failure can be excluded as the cause of hypothyroidism (*vide* Miss Ev., Case III).

(2) *Adrenal Function*

(*a*) The measurement of 17-ketosteroid excretion was of little value in separating the two conditions because an excretion rate of less than 2 mg. per twenty-four hours was also a common finding in patients with primary myxœdema (confirming Statland and Lerman, 1950).

(*b*) *The water diuresis test* was of considerable diagnostic value. We used a standard procedure which measured the rate of urine flow during the second hour after ingestion of 20 ml. water per kilogram of body weight and the percentage of the water dose excreted in three hours (Garrod, 1954). In 12 of the 13 cases of hypopituitarism, these values were less than 1·5 ml. per minute and 20% respectively. In the 18 cases of primary myxœdema not in heart failure[1], these values exceeded 3 ml. per minute and 50% excretion respectively in 16 cases, and only one excreted less than 25% of the water dose. In 1 of the 2 patients with a poor diuresis, this was restored to normal by thyroxine alone, and in the other it did not improve after cortisone. In 10 cases of hypopituitarism, when the test was repeated three hours after 50 mg. of oral cortisone, all excreted more than 40% of the water dose in three hours.

(*c*) *Insulin tolerance test* (Fraser and Smith, 1941).—6 of 8 patients with primary myxœdema showed hypoglycæmic unresponsiveness usually associated with a delayed fall in blood sugar. Because there was also a delayed fall in 2 patients with hypopituitary myxœdema, this test was of limited value in separating the two conditions.

(*d*) *Electrocardiogram.*—All the patients with hypopituitarism showed depressed or biphasic T waves, and in most of them the voltage was reduced throughout. Only when thyroid function was adequate by other tests could these changes be corrected by cortisone alone; otherwise thyroxine was also necessary. In primary myxœdema the ECG was corrected by thryoxine alone.

(*e*) *Plasma 17-hydroxycorticosteroid concentrations.*—These were measured by Dr. R. I. S. Bayliss (Bayliss and Steinbeck, 1953). In all 8 cases of primary myxœdema, they were within the normal range. In 8 cases of hypopituitarism, the levels were subnormal in 5, low normal in 1 and normal in 2 (1 of these showed no evidence of adrenal failure when on thyroxine).

(3) *Thyroid Function*

(*a*) *Basal metabolic rate.*—In the presence of pituitary or adrenal failure, a moderately low B.M.R., e.g. −20%, does not necessarily indicate hypothyroidism. Only in the 9 cases of hypopituitarism with obvious myxœdema was the B.M.R. less than −24%.

(*b*) *Radio-iodine tests.*—The urinary excretion and neck uptake of I^{131} were measured before and after administration of thyrotrophic hormone (T.S.H.)[2] (Querido and Stanbury, 1950) and the results compared with those obtained in subjects with normal thyroid function. 9 patients with primary myxœdema showed no significant neck uptake and no diminution in urinary excretion of I^{131} after T.S.H. However, 3 out of 6 patients with hypopituitary myxœdema also showed no significant response to T.S.H. (Ambinon B in 2 cases, Thyropar in 1 case). This failure of response could be due to secondary fibrosis of the thyroid gland such as Sheehan observed at autopsy in 15 out of 82 cases of hypopituitarism (Sheehan and Summers, 1949). The diagnostic value of this test is thus limited to excluding primary myxœdema if the neck uptake is significantly increased after T.S.H.; a negative response does not exclude hypopituitarism from being the cause of myxœdema.

(*c*) *Plasma cholesterol.*—In only 3 out of 9 cases of hypopituitary myxœdema did the plasma cholesterol exceed 300 mg.%.

[1]Congestive heart failure inhibits water diuresis.

[2]We used 2 preparations of T.S.H.: (1) Ambinon B (Organon), 2 c.c. by intramuscular injection three or four times a day for four days, and (2) Thyropar (Armour), 10 U.S.P. units once by intramuscular injection. The second dose of I^{131} was given on the last day of the Ambinon injections or forty-eight hours after the Thyropar injection.

(*d*) *Electrocardiogram.*—In primary myxœdema the ECG voltage was restored to normal by thyroxine alone, whereas in hypopituitary myxœdema cortisone, as well as thyroxine, was needed to obtain this effect. In general, cortisone and thyroxine were found to have a synergistic action in correcting the ECG changes in hypopituitarism.

(*e*) *Assay of thyrotrophic hormone in the blood.*—At the beginning of these studies, we hoped that by estimating T.S.H. in the blood (Gilliland and Strudwick, 1953) we would be able to obtain a clear indication of the site of the lesion. Cases of undoubted primary myxœdema were found to have a high serum T.S.H. level, whereas in 3 cases of Simmonds' disease this assay was negative. However, we then found a case (Miss Ev., Case III) of severe primary myxœdema with no measurable T.S.H. in her serum before treatment. After partial treatment with thyroxine a further test showed T.S.H. to be present in amounts comparable with those found in other cases of primary myxœdema. This patient also had a negative urinary F.S.H. assay which rose to post-menopausal levels after treatment with thyroxine.

Illustrative Examples

The following 3 cases illustrate some of the diagnostic difficulties. *Case I*, A. T., is a man of 45 who three years previously had begun to notice a loss of libido and sexual hair and to develop symptoms of myxœdema. Three years later the clinical and laboratory findings were as follows:

(1) *Gonadal function* (abnormal)
- (*a*) Eunuchoid skin
- (*b*) Loss of sexual hair
- (*c*) Small penis and prostate
- (*d*) Urinary F.S.H. excretion, positive to 4[1] and negative to 12 mouse units per twenty-four hours

(2) *Adrenocortical function* (probably normal)
- (*a*) 17-ketosteroid excretion, 5·5 and 7 mg. per twenty-four hours
- (*b*) Insulin tolerance test, normal
- (*c*) Water diuresis, abnormal on only 1 out of 4 occasions
- (*d*) Plasma 17-hydroxycorticosteroids, normal
- (*e*) ECG, low voltage and flat T waves

(3) *Thyroid function* (abnormal)
- (*a*) Clinically obvious myxœdema
- (*b*) B.M.R., −27%
- (*c*) ECG, low voltage and flat T waves
- (*d*) I^{131} tests, in hypothyroid range, but becoming hyperthyroid after T.S.H., thereby excluding primary myxœdema

This man is unusual in that he shows a failure of gonadotrophic and thyrotrophic function, without apparent adrenotrophic failure. The cause of the hypopituitarism could not be established.

Case II, Mrs. Br., aged 53, is an example of severe hypopituitarism with myxœdema. At 39 she had a post-partum hæmorrhage followed by a failure of lactation. Later menstruation returned and continued normally until the menopause at 51. She then developed myxœdema. The findings two years later (aged 53) are summarized below:

(1) *Gonadal function* (abnormal)
- (*a*) Loss of sexual hair
- (*b*) Urinary F.S.H. excretion, less than 4 mouse units per twenty-four hours

(2) *Adrenocortical function* (abnormal)
- (*a*) 17-ketosteroid excretion, 0·9 mg. per twenty-four hours
- (*b*) Water retention crises } with "hypopituitary coma"
- (*c*) Sodium depletion crisis }
- (*d*) Insulin tolerance test, delayed fall and hypoglycæmic unresponsiveness
- (*e*) Water diuresis, abnormal, corrected by cortisone
- (*f*) Plasma 17-hydroxycorticosteroids, nil
- (*g*) Urine 17-hydroxycorticosteroids, trace only
- (*h*) Electrocardiogram, abnormal (corrected by cortisone plus thyroxine)

(3) *Thyroid function* (abnormal)
- (*a*) Electrocardiogram, abnormal (corrected by cortisone plus thyroxine)
- (*b*) B.M.R., −48%
- (*c*) Plasma cholesterol, 297 mg. per 100 ml.
- (*d*) I^{131} tests, in hypothyroid range, with no response to T.S.H. (on 2 occasions)
- (*e*) Blood T.S.H. assay, negative

This result was obtained during administration of Ambinon B, which contains a small quantity of gonadotrophin, and is therefore probably not significant. If the hypogonadism had been primary, the F.S.H. excretion should have been high.

Despite the absence of symptoms for twelve years after the post-partum hæmorrhage, there is now evidence of severe panhypopituitarism. We would suggest that pituitary necrosis was incomplete but that the onset, perhaps coincidentally, of myxœdema, which remained untreated for two years, caused further damage to the surviving pituitary cells.

Case III, Miss Ev., is a nulliparous spinster of 58 who was found to have reversible anterior pituitary failure, due apparently to severe neglected primary myxœdema. Menstruation began at 17, ceased at 47 and was always scanty and infrequent. At 36 she suffered a severe head injury followed by prolonged unconsciousness. There is no record of a fractured skull, and skull X-rays (1953) were normal. The findings before treatment was started in 1953 were as follows:

(1) *Gonadal function* (abnormal)
  (*a*) No axillary, scanty pubic, hair
  (*b*) F.S.H. excretion, less than 4 mouse units per twenty-four hours

(2) *Adrenocortical function* (abnormal)
  (*a*) 17-ketosteroid excretion, 2·3 mg. per twenty-four hours
  (*b*) Insulin tolerance test, marked hypoglycæmic unresponsiveness before and after thyroid therapy
  (*c*) Water diuresis, only slightly subnormal and not further improved by cortisone or thyroxine
  (*d*) ECG, low voltage and flattened T waves, becoming normal with thyroid treatment alone

(3) *Thyroid function* (abnormal)
  (*a*) ECG, low voltage and flattened T waves, becoming normal with thyroid treatment alone
  (*b*) B.M.R., −54%
  (*c*) Plasma cholesterol, 320 mg. per 100 ml.
  (*d*) I^{131} tests, in hypothyroid range, with no response to T.S.H.
  (*e*) Blood T.S.H. assay, negative

One year later she was readmitted to hospital in moderate relapse, having neglected to take thyroxine for at least seven weeks. On further investigation, after two weeks of thyroxine at low dosage (0·1 mg. per day) she had an F.S.H. excretion of more than 24 mouse units per twenty-four hours, a high serum T.S.H. level, and a normal plasma 17-hydroxycorticosteroid concentration. This case illustrates how anterior pituitary function can be depressed in the presence of severe untreated myxœdema. Analogous findings have been reported in the experimental animal with untreated myxœdema (Starr *et al.*, 1939).

Conclusions

These studies have confirmed the occasional difficulty in distinguishing between primary and hypopituitary myxœdema, and have shown that severe myxœdema *per se* may inhibit the secretion of trophic hormones by the pituitary.

A water diuresis test, repeated when necessary after cortisone, was found, in the absence of heart failure, to be of value in distinguishing between primary and hypopituitary myxœdema, and should be used whenever the diagnosis is in doubt.

Acknowledgment

Our thanks are due to Dr. Russell Fraser under whose care and encouragement most of these patients were studied.

It is hoped to publish this material in full in the near future.

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Dr. M. Reiss and Dr. C. P. Haigh (Biochemical and Endocrinological Research Department of Bristol Mental Hospitals):

Various Forms of Hypothyroidism in Mental Disorder

The clinical diagnosis of hypothyroidism is frequently overlooked. This is because the degree of severity of the characteristic symptoms varies considerably. Between the clinically obvious hypothyroid state and the normal there is a kind of no-man's-land in which the true or effective level of thyroid activity is not easily decided. Whether or not this region can be investigated depends on the technical methods available for measuring thyroid function, as a purely clinical assessment appears impossible. Even with present laboratory methods, such as those depending on radio-iodine, which result in a numerical expression of thyroid activity, there is the well-known difficulty of deciding the significance of the intermediate values and, indeed, of showing any such significance to be unique.

Our radioactive tracer method (Haigh and Reiss, 1950; Reiss *et al.*, 1952; Haigh *et al.*, 1954) involves measuring (i) the almost linear rate of uptake, k, by the thyroid which is established during the hour following intravenous application of I^{131}, and (ii) the total forty-eight-hour urinary excretion, E_{48}, or, more usually and preferably, the twenty-four-hour uptake, U_{24}, of radio-iodine. U_{24} is measured conveniently with a toroidal counter (Haigh, 1951). From these measurements a further index of thyroid activity, I_t, is computed, defined as k/E_{48} or $k/(90\text{-}U_{24})$, the latter being preferred since urine collections tend to be uncertain (Haigh *et al.*, 1954). In general, k, U_{24} and I_t increase, and E_{48} decreases, when thyroid activity rises (Figs. 1 and 2).

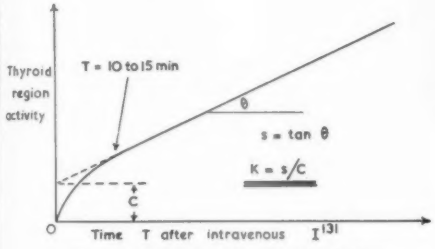

FIG. 1.—Computation of the k index.

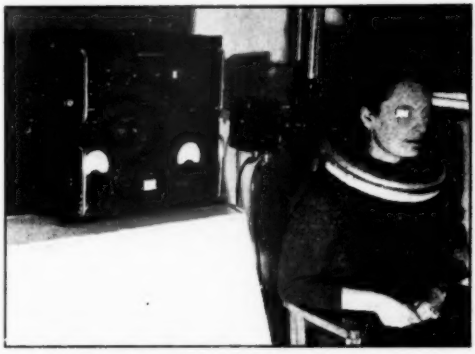

FIG. 2.—Use of toroidal counter to measure thyroid uptake of radio-iodine.

When a cross-section of a mental hospital population is examined by this method the result is of the type shown in Fig. 3 in which attention is concentrated solely on the index I_t. Log I_t is approxi-

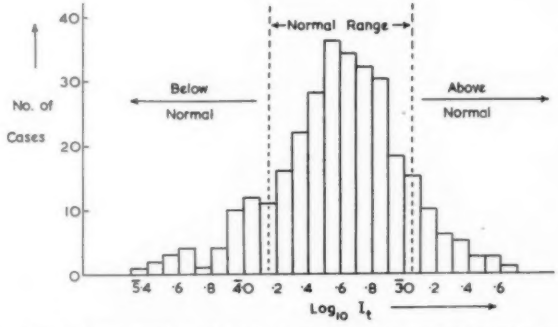

FIG. 3.—Typical distribution of Log_{10} I_t values from mental hospital patients.

mally normally distributed and, although a large proportion of the values from patients lie within the limits contained by normal control values, an appreciable number fall outside. Some of these

are cases of clinical hyper- and hypo-thyrosis, but others fall into the no-man's-land where classification can be attempted only on the basis of the numerical index. For the present purpose it is sufficient to adopt a crude classification of patients into three divisions, namely, those giving values within a normal range decided by measurements on normal controls and those with values above and below this range. Even with this rough criterion some error in classification results from the diffuse nature of the boundaries. Table I shows the distribution of patients within the 3 categories during three successive years.

TABLE I

Year		Total No.	% normal	% below normal	% above normal
1951	Male	201	69	15	16
	Female	220	64	15	21
1952	Male	244	66	20	14
	Female	332	67	19	14
1953	Male	246	67	17	16
	Female	296	67	15	18
Total	Male	691	67	18	15
	Female	848	66	16	18

Considering the range of thyroid activity below normal, first of all there is true hypothyroidism of primary or secondary origin. This usually gives I_t, k and U_{24} values greatly displaced from the normal, and it is assessed with corresponding ease. The primary may be differentiated from the secondary following radioactive measurements before and after treatment with thyrotrophic hormone. Within error, primary hypothyroidism gives the same values of k, E_{48}, U_{24} and I_t on each occasion whilst the secondary type shows an increased uptake and a reduced excretion of radio-iodine after thyrotrophic hormone has been given (Fig. 4).

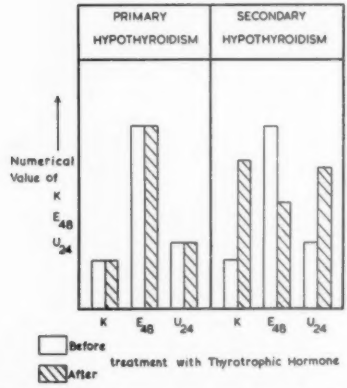

FIG. 4.—Differentiation of primary and secondary hypothyroidism.

Quite apart from the difficulty of correlating different levels of thyroid activity with measured numerical values, especially in the intermediate region, there are two types of cases in which the meaning of the radioactive measurements is not immediately apparent. In the first, the patient has I_t, k and U_{24} values in the normal or the above normal ranges, but the measured basal metabolism is low and frequently so low that its validity is not in question despite large possible errors which so often discredit B.M.R. measurements. Occasionally, such patients show some clinical symptoms of hypothyroidism. When an index of thyroid activity measured radioactively, such as I_t, is plotted against B.M.R., the two are seen to be simply related within reasonable limits and the cases of

peripheral insensitivity or effective hypothyroidism, not revealed by radio-iodine alone, stand out quite clearly (Fig. 5).

There is thus a peripheral insensitivity to thyroid hormone and the patient is, in effect, suffering from hypothyroidism despite the normal functioning of the thyroid gland. Treatment with large amounts of thyroid extract does not increase the oxygen consumption, a not unexpected phenomenon on account of the insensitivity of the tissues to the endogenously produced thyroid hormone. Langfeldt (1926) and Hoskins and Sleeper (1929) have already described a series of schizophrenic patients, who showed no increase in the B.M.R. even after high doses of thyroid. We did not find this form of tissue hypothyroidism restricted to schizophrenic cases only.

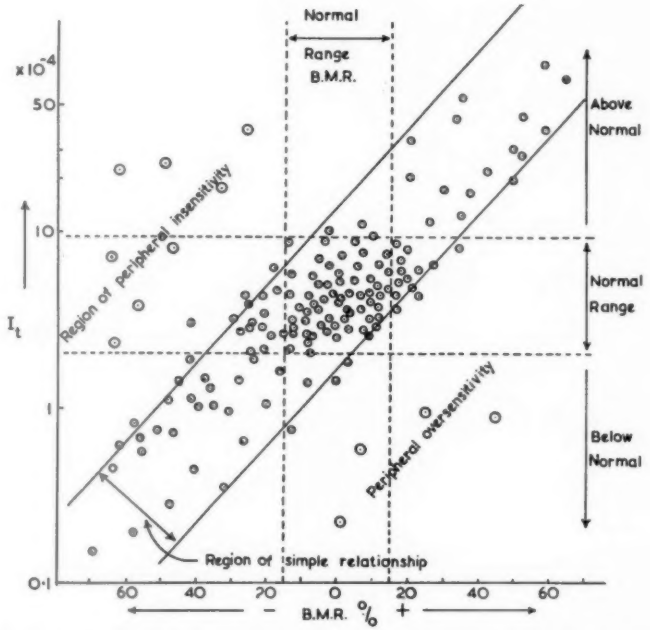

FIG. 5.—Relation of B.M.R. to I_t showing how cases of peripheral insensitivity to thyroid hormone fall outside the simple relationship.

In some of these cases radioactive measurements give values in the hyperthyroid range, presumably due to a feedback mechanism whereby low utilization of thyroid hormone by the tissues causes an increased secretion of thyrotrophic hormone by the pituitary anterior lobe. In this way a secondary hyperthyroidism is produced.

The foregoing type of hypothyroidism was revealed by the inconsistency of two types of measurement. The second type, which we have termed " pseudo-hypothyroidism", became apparent from discrepancies between the different radioactive measurements alone. It is characterized by a very low (sometimes zero) rate of iodine uptake during the first hour (k), but a normal or even increased twenty-four-hour uptake, U_{24}. The k value indicates hypothyroidism which cannot be true on the basis of the later measurement. This contradiction arises particularly with apprehensive patients and those suffering from some form of anxiety neurosis. Later, when the tension relaxes, the thyroid is able to operate in its customary manner to accumulate the normal amount of radio-iodine measured twenty-four hours after the injection. Thus, it seems that hypothyroidism cannot be assessed reliably from radioactive measurements made shortly after the application of radio-iodine, and this fact should not be overlooked, especially in techniques such as the early thyroid clearance method of Person *et al.* (1952).

The uptake curves measured in "pseudo-hypothyroidism" are demonstrated in Fig. 6: (i) shows a normal curve and the corresponding twenty-four-hour uptake; (ii) is a typical pseudo-hypothyroid

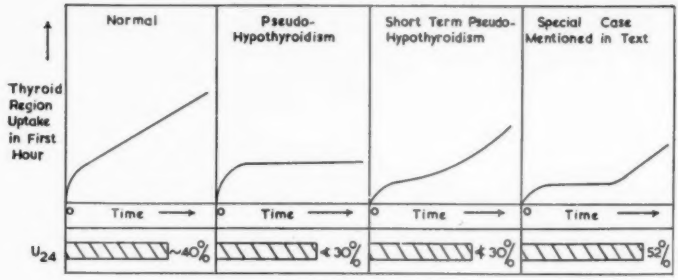

FIG. 6.—Characteristics of pseudo-hypothyroidism.

TABLE II.—PATIENTS WITH INITIALLY DECREASED THYROID FUNCTION

Group No.	Total No.	Thyroid activity after treatment	Mental state after treatment: Improved	Mental state after treatment: Not improved	Groups compared	χ^2	p
I	11	Unchanged	2	9			
	5	Decreased further ..	0	5			
II	10	Increased, but still below normal range.. ..	7	3	II-I	9·70	< 0·01
	10	Increased to above normal range	7	3			
III	59	Increased to normal range	57	2	III-I	48·16	< 0·001

TABLE III.—TREATMENT WITH THYROTROPHIC HORMONE. (ALL PATIENTS HYPOTHYROTIC BEFORE TREATMENT)

Mental conditions treated Diagnosis	No.	Changes in thyroid activity after treatment (No. of patients/No. showing improvement): Unchanged	Further decreased	Increased but still below normal range	Increased to normal range	Increased to above normal range
Endogenous depression ..	4		1/0		3/3	
Involutional depression ..	1	1/0				
Reactive depression	7			1/0	4/4	2/1
Schizophrenia	2				2/2	
Senile psychosis	1				1/1	
Anxiety reaction	4				4/4	
Obsessive compulsive reaction	1				1/1	
Hysterical reaction	1					1/0
Unspecified psychosis ..	2		1/0		1/0	

Group No.	Total No.	State of thyroid activity at end of treatment	Mental state after thyrotrophic hormone: Improved	Mental state after thyrotrophic hormone: Not improved	Groups compared	χ^2	p
I	16	Normal range	15	1	I-II	11·01	0·001
	4	Changing towards normal range	1	3	—	—	—
II	3	Remaining outside normal range or deteriorating	0	3			

response where the rate of accumulation is zero after the count due to radio-iodine in the blood vessels has been established; (iii) is a less severe case in which accumulation began rather later than is normal, and (iv) is a special case where a very apprehensive patient was reassured by the technician some time after the measurement was commenced.

This discrepancy between the I^{131} uptake during the first hour and the total twenty-four-hour uptake rate is thought to result from an increased mobilization and circulation of vasoconstrictor substances when the patient attends for the first part of the investigation. In fact, uptake curves similar to those of Fig. 6 can be obtained from nembutalized rabbits after continuous infusion, or injection, of small doses of adrenaline (Haigh *et al.*, 1954). In other experiments, different forms of stress very rapidly reduced by 50% to 80% the I^{131} uptake of the thyroid of normal and hypophysectomized rats. A similar action was observed after injection of small adrenaline doses (Badrick *et al.*, 1954).

Using this particular method of thyroid activity measurement we have been able, as mentioned above, to detect many cases of intermediate hypothyroidism in a psychiatric hospital population. It has also been possible to study relations between thyroid and mental disturbances and, in particular, to relate changes in mentation of patients undergoing various forms of treatment with the accompanying changes in thyroid activity. The results shown in Table II reveal a significant correlation between improvement in mental state and normalization of thyroid activity in 95 originally hypothyrotic patients. This was regardless of the type of treatment applied. Table III concerns patients with hypothyroidism treated with thyrotrophic hormone. In cases of secondary hypothyroidism this normalizes the thyroid activity and there is a significant correlation between this process and the accompanying mental improvement, regardless of the psychiatric disease entity concerned.

Summary

Following radioactive assessment, the thyroid activities of mental hospital patients have been placed in three categories: normal, above and below normal. On the average 17% of all cases fall into the lower range. True hypothyroidism gives thyroid index values greatly displaced from the normal and its primary or secondary origin may be determined by subsidiary measurements.

In two types of cases the meaning of the radioactive measurements is not readily apparent:

(1) Cases in which there is a peripheral or tissue insensitivity to thyroid hormone causing an effective hypothyroidism, although the measured thyroid activity may be normal or above normal.

(2) Cases of "pseudo-hypothyroidism" mainly evident in apprehensive patients and characterized by a low thyroid uptake of radio-iodine measured shortly after the application of the tracer, and a twenty-four-hour uptake value not below normal. This is believed due to an increased circulation of vasoconstrictor substances during the early measurements.

A correlation exists between changes in thyroid activity and in mentation.

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[*April* 28, 1954]

The following cases were shown:

Three Cases of Male Iso-Sexual Precocity (Pseudo-Puberty) Associated with Adrenal Enlargement.—Mr. A. F. BROMWICH, with Dr. B. CAMBER, and Dr. J. ADLER, for Mr. L. R. BROSTER.

Graves' Disease, with Lifelong Unilateral Exophthalmos.—Dr. I. C. GILLILAND.

Hypopituitary Dwarfism Due to Craniopharyngioma.—Dr. OLIVER GARROD.

Osteoporosis and Hypogonadism.—Mr. W. H. STEPHENSON, and Dr. R. I. S. BAYLISS.

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Section of Obstetrics and Gynæcology

President—VICTOR LACK, F.R.C.P., F.R.C.S.Ed., F.R.C.O.G.

[*March* 26, 1954]

DISCUSSION ON CARCINOMA OF THE BODY OF THE UTERUS

Mr. C. W. A. Kimbell: In a review of the records of this Section since 1900, I can find only three major previous discussions on carcinoma of the body of the uterus (*see* Donald and Shaw, 1929; Strachan, 1930; Hurdon and Chambers, 1933; *see also* Palmer, 1928).

It would seem advisable to review the present position since, while carcinoma of the cervix is much to the fore, carcinoma of the body of the uterus has received less attention, and this situation may be associated with a dangerous sense of complacency. It is probably true to say that this lesion is, in the main, still being treated by total hysterectomy and removal of adnexa, at times followed by radium or X-ray therapy.

My remarks are based on a study of 245 cases (Samaritan Hospital, 183; Prince of Wales's Hospital, 62) occurring from 1938 to 1953 inclusive (sixteen years).

The incidence of carcinoma of the corpus would appear to be increasing. Analysis of female deaths in England and Wales for the five-year period ending 1952 shows, in the last three years, roughly 2 cervix cases to 1 corpus. Kottmeier (1953) states the proportion to be 2·4 to 1. Randall (1945) finds 4·5 to 1 in the 45–55 age group, but parity in the 70–75 age group. Way (1951) finds 7 cervix cases to one body admitted for treatment; he quotes Stallworthy of Oxford as giving a figure of 2 to 1.

Age.—Although carcinoma of the corpus occurs principally in the postmenopausal patient, in this series 20·8% (51 in 245) were premenopausal; the majority were between 50 and 70 (188 of 245). It is worthy of note that 4 cases occurred before 40 (30, 34, 38 and 38). Donald and Shaw (1929) found only 1·3% were premenopausal; McCullagh (1929) reported 5·79% under 40; Dearnley (1949) found 31% were premenopausal, Novak (1947) 34%, and Rickford (1953) 20%.

Age of onset of the menopause.—In 173 cases of known age 49·5 years was the average. The literature states 46–48 years. The Medical Women's Federation in 1933 found 71% (966 women) ceasing to menstruate before 50. In the present series 64·1% had a menopause at 50 or over.

Randall (1945) states that 35% of women ultimately developing adenocarcinoma of the fundus have continued their normal periods past the 50th year, as compared with 8% in the control group. Crossen and Hobbs (1935) drew attention to the fact that in cases of carcinoma of the fundus menstruation ceased later than in normal women, and this opinion is generally accepted to-day.

Parity.—In this series 60 cases were multiparous in 227 where the information was available (26%). Dearnley (1949) found 11·6% to be multiparous, and Crossen (1946) found 38% (*cf.* cervical cancer 1–10%).

Ætiology.—Stilbœstrol in relieving the menopause should be used with caution and should not be prolonged.

Fibromyomata: It is difficult to know the true incidence of fibroids in the general population. In carcinoma of the corpus 25–33% of cases are associated with fibroids according to the literature. In this series fibroids were only noted in 11 cases, clearly due to inadequate notes.

Obesity was noted in 16 cases, but doubtless was more common. Way (1954) stresses that weight and height must be considered together; he found 44 obese cases in 88. Obesity is clearly allied with hypertension and diabetes, and these three conditions are commonly associated with carcinoma of the body.

Previous radiotherapy had been given in 7 cases: Radium twenty-five, twenty, fifteen, six and four years before; X-ray twenty-one and seven years before.

Diabetes was noted in only 4 cases. In the literature the association is stated as much commoner: Scheffey *et al.* (1943) give 11%; Moss (1947), using glucose tolerance tests, found 11 in 23 cases; Palmer *et al.* (1949) in 165 consecutive cases found 16·9%; Way (1954) in 106 cases, using glucose tolerance studies, found 29% diabetic. Many other cases show a prediabetic type of curve. Spiegelman and Marks (1946) found an incidence of 1·02% in 1,300,399 females over 35. As Way says, on this estimate clinical and subclinical diabetes would be 28·4 times as common in his series of cases as in the general population.

Way (1954) suggests that there is some evidence to show that over-activity of the anterior pituitary as judged by fibroids, diabetes, &c., occurs, and that this factor may be hereditary.

Symptoms.—Almost exclusively carcinoma of the corpus declares its presence by postmenopausal bleeding, varying from a "show" to frank loss. Bleeding may be late and the findings extensive. In others discharge often tinged with blood or purulent discharge from a pyometra may be present. Pain is unusual except in extension outside the uterus, with sometimes large fixed pelvic tumours, or when the corpus is distended by blood or pus. In some 20% where the lesion is premenopausal

CT.

irregular or prolonged bleeding is the presenting symptom. If we exclude cases of three-, four- and five-year symptoms as stated in the records the average duration of symptoms was 7·05 months.

Diagnosis.—Diagnostic curettage is indicated in any increased or prolonged bleeding premenstrually, especially in women continuing to menstruate after 50. It is also indicated in any postmenopausal case even if an obvious cause such as senile vaginitis, caruncle or polyp is found. Section, biopsy or smear examination, whilst valuable in experienced hands, should not replace diagnostic curettage. Hysterography is used by some who state that the risk of spread is only theoretical. Such studies show that cervical involvement is more common than is believed. Heyman (1936) urged the value of fractional curettage, the resulting specimens being kept for separate examination. It is common experience that the insertion of a dilator is followed by a gush of tumour tissue, the exact origin of which is difficult to assess.

In a study of 780 cases Heyman found 172 (18%) involving corpus and cervix. Leissner (1950) found 22% in a most careful examination of specimens. The site of origin is clearly important as regards choice of treatment, as those cases in which the cervix is involved will be associated with a very different spread. In the present series few such cases were noted. One case was diagnosed only at post-mortem examination after admission to the medical wards in a state of great emaciation. Several cases were found at laparotomy for pelvic tumours. A few cases were found after vaginal hysterectomy for procidentia.

Finn (1952), reviewing 299 cases, found that errors in diagnosis include: (1) Failure to investigate irregular bleeding in a woman still menstruating. (2) Correction of only obvious cause of postmenopausal bleeding. (3) Disregard of significance of perforation in older women. (4) Failure to curette when cervical stenosis is dilated and hæmatometra drained. (5) Reliance on smears for diagnosis. (6) Complete reliance on endometrial biopsy. (7) Inadequate curettage.

To this list I would add (8) Failure to perform endometrial biopsy in cases receiving œstrogen therapy where treatment has ceased and bleeding continues.

Treatment.—The main methods are as follows: (1) Abdominal total hysterectomy and removal of tubes and ovaries with or without pre- or post-operative radiotherapy.

(2) Vaginal hysterectomy—notably by Professor Bastiaanse.

(3) Radium therapy—notably at the Radiumhemmet, Stockholm, with operation for failed cases.

Clearly the question of the general state of the patient such as age and infirmity, gross obesity, cardiovascular disease, respiratory disease, will influence choice of treatment. Some patients refuse operation or any treatment. A small group are found to be inoperable at laparotomy. Finally, the site of origin of the growth is important.

To compare results there must be some form of international agreement. Many classifications have been suggested. That of Professor Heyman and the Editorial Committee of the Annual Report (1953) clearly should be in general use.

Operation alone: Several rules should guide us. (1) The cervix is sutured; this can be difficult. The cervical occlusive clamp designed by Mr. R. Percival (1952) is worthy of note since it is easy of application and there is no spill (*see* p. 906). (2) Ligature of the ends of the tubes is advised. (3) Gentleness in handling of the uterus. Despite all this care, the uterus can be so rotten that it ruptures and there are the rules brought to nought.

Whether operation should be proceeded with at once after diagnostic curettage or postponed one week because of disturbance of cells, I do not know.

The operability rate in this series was 90% (221 in 245 cases). Mortality was 6 in 221 cases, i.e. 2·7%: pulmonary embolism occurred in 3, post-operative collapse in 1, infection (died twenty-fifth day) in 1 patient who had had pre-operative radium, and uræmia in 1.

Vaginal hysterectomy.—This is the method of elective treatment by Professor Bastiaanse (personal communication). I have details of 262 cases by the vaginal route and 35 by the abdominal route. There was one death in 297 cases. The operability rate was 94·9%. In a series of 115 cases one or both ovaries could not be removed in 28·7%.

Radium.—Professor Heyman and his colleagues have made an outstanding contribution. Hysterectomy is reserved for cases in which there is failure of radiotherapy, or in which intracavity radium is not suitable. Dr. Lederman will describe in greater detail the Stockholm technique and results.

Results.—It is very difficult to obtain from the literature truly comparable series of cases. An international classification is a vital need.

RADIUMHEMMET

1936–45	855 cases	480 alive and no evidence of disease	Five-year apparent cure rate 56·1%
1936–40	356 cases	149 alive after ten years no evidence of disease	Ten-year apparent cure rate 41·9%

AMSTERDAM

1.1.39–1.1.49	190 cases	Five-year cure rate in 119 cases	62·6%
1.1.39–1.1.44	88 cases	Ten-year cure rate in 51 cases	58·0%

It is not possible to quote the 1952 survey of cancer in London in which 321 cases of cancer of the corpus uteri are reviewed, as 18 sarcoma and chorion carcinoma are included.

In my series there were 2 fatalities due to perforation of the uterine wall, 1 death from pelvic abscess after radium and 2 deaths from pelvic peritonitis after radium and radiotherapy.

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Mr. W. R. Winterton (Middlesex Hospital): Carcinoma corpus uteri has been considered relatively so benign a growth compared with cancer elsewhere that we have been too easily satisfied with the results of treatment. Most of the published results show 60–70% five-year survivals, that is, between 30 and 40% of the cases will die of the disease within five years of treatment, and still more within ten years.

Thus it has become the usual practice to perform the minimal operation for this cancer, instead of wide removal.

It must also be remembered that as a general rule only the better series are published. It can therefore be assumed that the five-year survival rate generally is lower.

I have examined the notes of four hospitals from 1930 onwards mostly from the Middlesex Hospital. These include every case of carcinoma corpus uteri together with many inoperable cases from other hospitals sent for palliative radiotherapy. The 350 cases represent the results from over twenty different surgeons and can therefore be considered a completely impersonal series; the five-year survival rate is almost exactly 50%. I have taken a five-year survival rate for convenience, but I would stress that five years is inadequate. Many of these patients are old and cancer grows more slowly in old people. A number of cases who survived five years later developed recurrences, the longest time being a recurrence in the vault twelve years after a total hysterectomy.

Diagnosis.—The symptoms of carcinoma of the body are bleeding and sometimes a serous discharge, and as a general rule the symptoms arise late in the disease. The growth is enclosed in the uterus where it is comparatively free from trauma and free from infection, and consequently the growth often continues for a long period before it begins to break down and give rise to bleeding. Regular menstruation and the presence of a carcinoma are not incompatible. As evidence of this delay we frequently find the endometrial surface of the uterus entirely replaced by growth although there is only a short history of bleeding.

Though the textbooks tell us that the growth is rare before the age of 50, I was surprised to find in this series of 350 cases that nearly 20% were under 50. The ages of my own personal series varied from 27 to 85, with an average age of 56.

Most of us agree that a diagnostic curettage is necessary, but there is a school of thought which considers it dangerous and liable to spread the growth. There is also a school of thought which stresses the importance of fractional curettage in order to determine the exact site of the growth. It is, of course, important to distinguish between a cervical and a corporeal growth, but anything more than that is likely to be inaccurate and of little value. Frequently the growth seems to pour out of the cervix as soon as the cavity of the uterus is entered.

For the last twelve years I have been doing an operation of the Wertheim type on these cases. I have operated on 90 cases, of which 61 were more than five years ago.

Of the 28 cases in which I have reports on the glands, in only 2 were they invaded. This is a small proportion but surely sufficient to warrant removal. It is argued that this extension of the operation adds to the mortality and morbidity. Of the 90 cases there were three operation deaths, an operative mortality of 3·5%. Many of these patients are old but in older patients the operation is less difficult. The tissue planes are easier to find and there is less bleeding. There were no urinary fistulæ but some of the patients were left with stress incontinence which is a not uncommon sequel to a Wertheim. Recently I have been doing a routine Everard Williams bladder fixation in an attempt to overcome this.

Operability rate.—So firmly do I regard surgery as the treatment of choice in this condition that operation has been attempted in every case except one. My oldest patient was 85 at the time of operation, which was rather less extensive than the routine. She is now 89 but is still too recent to be included in the follow-up series. My fattest patient weighed 20 st. and there were 2 of 17 st. No patient was refused operation on account of hypertension, heart disease or diabetes, for which I have to thank my loyal and efficient anæsthetists. The advances in anæsthesia and blood transfusion in the last fifteen years, and to a lesser extent the introduction of chemotherapy and antibiotics, have made this extension of the operation practicable. Previously the operative mortality would have been too great to be justifiable.

Going through this large series of notes since 1930 it is my impression that the number of advanced cases seen has much diminished in the last fifteen years.

My operability rate is high (95%) and only 1 patient was refused operation. She was a feeble 79 which in 1940 I considered too old. I find it difficult to understand why some series should include such a large proportion of inoperable cases. Many cases of carcinoma of the body are associated with fibroids and these may well be mistaken for extensions of the carcinoma. I consider that unless there is a distant metastasis such as a secondary in bone or one at the introitus of the vagina almost every case warrants a laparotomy and should not be considered inoperable until that has been done. It so happened that I was not faced with any cases of this kind.

Recurrences.—One of the major problems of carcinoma of the body of the uterus is the high incidence of recurrences in the scar of the vaginal vault. The Middlesex and Soho Hospital notes are not always sufficiently detailed to give the exact figure. Though the majority of recurrences are described as local, specific mention of recurrences in the scar of the vaginal vault occurs only too frequently. It is, however, impossible to give an accurate figure. In 1 case a vault recurrence appeared for the first time twelve years after operation.

How do these growths arise? There are three possible sources. Either there is lymphatic spread in the wall of the vagina, or it may be embolic, or it is a result of spill of cancer cells.

Lymphatic spread is probably responsible for the occurrence of secondaries at the introitus. These are, however, fairly uncommon, and the fact that in only 2 cases out of 28 was there invasion of the glands seems to demonstrate that lymphatic spread is unusual. Some American authors put the figure much higher and perhaps my figures are too small to be of great value.

Lymphatic spread, on the other hand, is unlikely to be the cause of vault recurrences. This is probably brought about by the spill of cancer cells during the operation. An interesting comparison may be made with the operation of restorative excision of the rectum. Here it was found that a common position for recurrences was the site of the junction and it was thought that cancer cells were stitched into the bowel wall. By putting a clamp on the bowel below the growth and washing out the bowel below this level with many pints of 1 in 5,000 perchloride of mercury which kills off cancer cells, the incidence of recurrences at this site was considerably reduced.

Embolic spread is responsible for bony metastasis of which there was one case in my series, occurring three years after operation.

There are a number of methods in common use to try and prevent this danger of cancer cell spill. Operation is postponed for a week after the diagnostic curettage to allow the cancer cells lying in the vagina to die. This I am sure is a wise precaution, and if an operation of the Wertheim type is being considered it is, of course, most important that histological confirmation of the growth be first obtained.

The cervix is stitched up as a preliminary to operation. This seems a very crude and unsatisfactory method. The manipulations of the uterus during its removal are likely to squeeze cells through a stitched-up cervix.

Pre-operative radium may be used. This must help, provided an adequate dose is given, but it is essential that the dose is truly adequate. I have no experience of this but I intend to adopt it in the future.

For some years I have put a pack in the upper third of the vagina and then a full pack below this. At the stage of the operation when the vagina is about to be divided, the lower pack is removed and a Bonney-Wertheim clamp, which is modified by having teeth like a Willett's scalp forceps, is put across the vagina below the upper pack and the vagina is divided below the clamp. By this method it is hoped that any cancer cells which have been squeezed out of the uterus during the manipulations of the operation will be caught by the pack and that none will reach the vagina which remains.

The commonest recurrence is the mass in the pelvis which frequently feels almost unattached to

surrounding structures. It is difficult to know exactly from what tissue it is arising. It may be in the lymphatics, although the glands are so rarely affected and the characteristics of the recurrence differ from that seen in cervical cancer where it arises in the glands on the side wall of the pelvis. This may be also due to the spill into the pelvic tissues during the operation. A year ago I had a case of recurrence involving two coils of ileum while the pelvis was completely free from growth, occurring eighteen months after operation. It is difficult to explain this by any way other than by spill. A certain number of patients are going to die of distant metastases whatever treatment is given to the pelvis. These are unavoidable with the present methods of treatment at our disposal, but there is ample scope by more careful attention to detail, by a more radical operation and by pre-operative sterilization of the growth by radiation to reduce the number of recurrences in the pelvis.

My own series consists of cases operated on since 1940 when I began to do a more radical operation. At first it consisted of removal of the parametrium to the side wall of the pelvis and including between half and two-thirds of the vagina. I did not take the glands. My reason for this type of operation was that in cases of cancer as wide a clearance as possible should be made. From 1948 I took the glands as well, not because I felt that a lymphadenectomy was important but because it gave a wider clearance and made hæmostasis easier. At the same time the small upper pack was used. In the case of very fat or very old patients a less radical operation was sometimes adopted, but these have not been separately classified.

Table I shows that 61 cases were seen between 1940 and 1948. One case was refused operation in

TABLE I

Cases seen 1940–1948	61	
Lost on follow-up after two years	1	
Died of intercurrent disease after one year	1	
Operable cases	57	93%
Operation deaths	2	3·5%
Recurrences	8	
Alive for five years	45	76%
Operable cases alive		82%

1940 because she was aged 79 and she was treated with radium. The other cases described as inoperable consisted of one case of alimentary tract invasion with fistula formation, which I attempted to operate on without complete removal and the patient died. In 2 cases there were plaques of growth on the rectum which to-day would have been treated by a posterior exenteration. In one of these a secondary at the introitus had been treated in 1942 with radium and the primary in the uterus was not diagnosed till 1946.

I am fortunate in that only one patient died of intercurrent disease, and only one was lost on follow-up. If I may leave these out in assessing the results it gives a 76% five-year survival rate or an 82% five-year survival rate if calculated on those cases where there was a complete macroscopic removal.

Table II gives the cases from 1940 to date. This is done in case it is argued that the operative mortality is likely to be high in what tends to be an elderly group. The figures of gland invasion are very incomplete, but they seem to indicate that the figure is low.

TABLE II

Cases seen 1940–1954	90	
Operability rate		95%
Operation deaths	3	
Glands sectioned	28	
Glands invaded	2	

Mr. R. B. K. Rickford (St. Thomas's Hospital and Chelsea Hospital for Women):

The Results of the Treatment of Carcinoma of the Uterus

This short communication is based upon a follow-up of all new cases seen at the Chelsea Hospital for Women, and St. Thomas's during the years 1943–1948, and it aims at showing what surgery can do in the treatment of this disease. All cases were proved histologically, and the follow-up was complete for the five-year period.

In this series there are a total of 147 cases, 99 at Chelsea, and 48 at St. Thomas's.

In the years 1949–1953 a further 174 cases have been treated and certain details of this subsequent series have been investigated. The total number of cases under review is therefore 321.

The total five-year survival rate is 92 patients out of the 147, or 62·4%, and 120 or 81·6% were treated by hysterectomy with or without radiotherapy. This compares very favourably with Heyman's 1937 figure of only 45·4% which he estimated to be "clinically operable". From 1949–1953, 152 out of 174 cases were treated by hysterectomy, some of which were radical operations, giving an operability of 87·4%. It has been found that with modern methods of anæsthesia there are now very few contra-indications to surgery.

TABLE I.—SUMMARY OF TOTAL CASES REVIEWED

1943–1948:
Chelsea Hospital for Women:
Total number of cases .. 99
Alive and well after five years 59
St. Thomas's Hospital:
Total number of cases .. 48
Alive and well after five years 33
Total 147
Alive and well 92
62·4%
Operability 81·6%

1949–1953:
Chelsea Hospital for Women:
Total number of cases .. 114
St. Thomas's Hospital:
Total number of cases .. 60
Hysterectomies 15.
Operability 87·4%

In view of the difficulty of analysing the results of the treatment of this disease, it has recently been suggested that a division should be made into four broad groups (Table II), depending on the extent of this disease, as follows:

A. Confined to the endometrium and uterine wall.
B. Endometrium and cervical canal.
C. Uterus and adnexæ.
D. Spread to the pelvis or distant metastases.

TABLE II

Group A	104	..	70·7%	
Group B	17	..	11·6%	29·3%
Group C	9	..	6·1%	
Group D	17	..	11·6%	

The five-year survival rates for these groups are shown in Table III. Analysis of 60 cases from 1949–1953 at St. Thomas's gives very similar results, as regards staging (*see* Table IV).

TABLE III

Group A ..	104	78 alive	75%
Group B ..	17	9 alive	53%
Group C ..	9	5 alive	55·5%
Group D ..	17	0 alive	0·0%

TABLE IV

Group A ..	..	45	75%
Group B ..	..	3	25%
Group C ..	..	7	
Group D ..	..	5	

The treatment adopted has been analysed and subdivided for cases falling into the various stages as follows:

TABLE V.—SUMMARY OF TREATMENT

	A			B			C			D		
	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead	Total	Alive	Dead
Total hysterectomy and bilateral salpingo-oophorectomy (B.S.O.)	64	53	11	8	4	4	2	1	1	6	0	6
Radium menopause. Total and B.S.O.	3	3	0	1	1	—	—	—	—	—	—	—
Total and B.S.O. + X-rays or radium for recurrence	16	12	4	2	2	—	4	4	—	1	—	1
Total and B.S.O. prophylactic vault radium ..	2	2	—	1	—	1	—	—	—	—	—	—
Radium + late hysterectomy	1	1	—	—	—	—	—	—	—	—	—	—
Subtotal and B.S.O. ..	4	3	1	—	—	—	1	—	1	—	—	—
Wertheim	—	—	—	3	2	1	—	—	—	—	—	—
Vaginal hysterectomy ..	1	1	0	—	—	—	—	—	—	—	—	—
Radium	12	3	9	2	—	2	—	—	—	4	—	4
Laparotomy	—	—	—	—	—	—	2	—	2	4	—	4
Nil	1 D. and C.	—	1	—	—	—	—	—	—	2	—	2
	104	78	26	17	9	8	9	5	4	17	0	17

From Table V it will be seen that 120 hysterectomies were carried out, a few with a menopausal dose of radium preceding operation, where the diagnosis had been in doubt, and a number with post-operative X-rays or radium either immediately or later for recurrences. 89 of these patients were alive and well five years later, or 74·2%.

64 patients were treated with a total hysterectomy and removal of both appendages and no subsequent radiotherapy was given, as the disease was strictly limited to the body of the uterus. 53 of these were alive and well five years later, or 82·8%, and 4 of those who did not survive died of intercurrent disease, 1 of cerebral hæmorrhage three years later, 1 of coronary thrombosis one year later, 1 of a second primary in the pancreas two years later, and 1 of lobar pneumonia and senility at two years.

This analysis gives a remarkably good picture of what can be done by surgery without pre-operative radium in the treatment of this disease. It had, however, been felt by many surgeons for some time that the incidence of recurrences particularly in the region of the vaginal vault was still very unsatisfactory. Various methods have been adopted to overcome this, and in the subsequent six years at these two hospitals 16 Wertheim's hysterectomies have been done, and 10 patients have had prophylactic vault radium inserted about fourteen days after operation.

Recurrences

A study of cases in Group A of this series of 321 had brought to light 13 recurrences, 11 of which were at the vaginal vault. 4 of these were present within three months, 3 within six months, 1 at a year, 1 at five years.

Reference to Table VI shows that the gross pathological type has no particular significance. The length of history of symptoms before treatment varies from two weeks to three years; but with one exception there had been extensive involvement of the endometrium when a recurrence occurred later.

Table VI.—Group A Recurrences after Total Hysterectomy and Bilateral Salpingo-Oophorectomy

Site	Time of discovery	Length of orig. hist. and symptoms	Pathology	Extent of disease at hysterectomy
Vault	3 months	5 weeks	Papillary	Extensive
Vault	12 months	4 months	Columnar	Upper part of body
			Columnar	
Vault scar	5 years	7 months	Papilliferous	Extensive
			Columnar	
Pelvic wall	6 months	2 months	Columnar with squamous metaplasia	Extensive
Vault	3½ years	6 months	Columnar	Extensive
Vault	3 months	6 months	Columnar	Extensive
Vault	6 months	18 months	Anaplastic	Extensive
Vault	6 months	18 months	Polypoid adenocarcinoma	Not recorded
Vault and para-aortic node	12 months	4 months	Adenocarcinoma	Cornual
Centre of pelvis	9 months	12 months	Adenocarcinoma	Fundus and isthmus
Vault	3 months	3 years	Columnar	Extensive
Vault and posterior vaginal wall	9 months	6 months	Adenocarcinoma	Extensive
Vault	9 years	1 month	Columnar adenocarcinoma	Extensive

There are two possible reasons for these vault recurrences. The first is the possibility that cancer cells are implanted in the operation site either by expression from the uterus during operation, or that viable malignant cells are already present in the vaginal canal at that time. Hence the practice of suturing the cervix, or packing the canal prior to operation, or the use of pre-operative intra-uterine radium, as is almost routine in the United States. The second possibility is that growth is already in the lymphatics of the parametrium. Strachan (1930) made similar observations at this Society.

The lymphatic drainage of the uterus has been studied on many occasions. Poirier (1903) describes the main drainage from the uterus being by three routes. Firstly via the ovarian vessels to the para-aortic nodes. Secondly, lymphatics run along the round ligaments to the inguinal glands. Thirdly, lymphatics from the lower part of the body of the uterus pass through the cardinal ligament to the internal iliac glands. Várady (1947) while carrying out a hysterogram inadvertently demonstrated the point when lymphatic emboli occurred. The lipiodol passed along the vessels at approximately 10 cm. an hour, and was demonstrated in the internal iliac glands in fifty minutes. No radio-opaque substance reached either the sacral or inguinal nodes.

Navert (1952) has made extensive studies of pelvic nodes removed when operating for carcinoma of the endometrium. He found that in 50 cases in which lymphadenectomy was carried out pelvic lymph nodes were positive for carcinoma in 14 (28%). He does not, however, state in which clinical group these cases were found.

It is, therefore, apparent that when the lower third of the endometrium is malignant, there is a distinct possibility of spread to the parametrial lymphatics, and it therefore follows that in such cases more extensive surgery may well be indicated.

However, a routine radical hysterectomy with bilateral lymphadenectomy for all cases would almost certainly so increase mortality and morbidity in this relatively elderly age group, as to defeat the object in view.

There is no doubt that when the cervical canal is involved radical surgery is essential. The problem is to decide which of the other cases require extensive excision.

It has been my practice during the last few years to attempt to assess the extent of endometrial involvement by fractional curettages, as originally described in Stockholm prior to packing the uterus with radium. When growth is present low down in the cavity a radical hysterectomy has been done if the patient is reasonably fit. One practical difficulty of fractional currettage is that occasionally on dilating the internal os growth oozes out of the uterus, and it is impossible to discover the extent of endometrial involvement; or at times there is a large polypoidal mass occupying the cavity of the uterus with a smallish base at the fundus and yet the curette obtains growth from just inside the os.

If it is considered that the patient is not fit for an extensive operation, a simple total hysterectomy followed by prophylactic vault radium has been used. Dobbie (1953) recently described apparatus which has given excellent results, and reduced the incidence of vaginal recurrences to negligible proportions, there being 2 only in 84 cases.

Tables VII and VIII give some details of the 17 Wertheim's hysterectomies done at the two Hospitals in the last five years.

TABLE VII.—WERTHEIM'S HYSTERECTOMIES

GROUP A	Age	Length of history	Extent of disease	Pathology	Glands
1	53	12 months	Deeply invasive. Almost whole endometrium	Adenocarcinoma. Well differentiated	Negative Parametrium just clear
2	63	18 months	Extensive to within ½ in. of internal os	Adenocarcinoma	Negative
3	64	7 months	Upper half of endometrium	Columnar	Negative
4	62	3 years	Extensive, almost to internal os	Papilliferous. Columnar	Negative
5	54	5 months	Thought to be endocervical at dilatation and curettage	Columnar. Adenocarcinoma	Negative
6	60	2 months	Extensive	Columnar	Negative
7	54	2 weeks	Whole endometrium. Deeply invasive	Columnar	Positive
8	59	18 months	Whole endometrium down to internal os. Invading muscle	Anaplastic	Negative

No deaths or fistulæ

TABLE VIII.—WERTHEIM'S HYSTERECTOMIES

GROUP B	Age	Length of history	Extent of disease	Pathology	Glands
1	42	6 months	Extensive down canal	Papilliferous adenocarcinoma	Negative
2	56	4 years	Whole endometrium and whole canal	Papilliferous adenocarcinoma	Negative
3	65	2 months	Extensive body and cervix	Columnar	Negative
4	52	12 months	Extensive into canal	Anaplastic	Negative
5	58	1 month	Extensive body and cervix	Adenocarcinoma	Positive
6	53	1 year	Extensive to below internal os	Adenocarcinoma. Slight anaplasia	Positive
7	65	1 year	Body and cervix	Adenocarcinoma	Iliac neg. Parametrial pos.
8	53	5 months	Body and cervix	Adenocarcinoma	Negative
GROUP D					
9	48	6 months	Body, cervix and pelvic peritoneum	Adenocarcinoma	Negative

Two post-operative deaths

It will be seen that glands were only positive once in Group A, and three times in Group B. The other point of interest shown is the extraordinarily short history that may be obtained even when the disease is far advanced.

SUMMARY

70 to 80% of Group A patients can be cured by simple total hysterectomy, and removal of the appendages. When the cervical canal is involved a radical hysterectomy is probably indicated.

Surgery will save a proportion of lives when the ovaries are already clinically involved, which would

not be possible with radiotherapy. I do not believe that with such good results radical hysterectomy in such an old age group should be contemplated as a routine, with its attendant morbidity, prolonged convalescence, and potential operative mortality. There is, however, a place for extended surgery when the growth has given rise to symptoms for a considerable time, and can be shown to involve the lower third of the endometrium.

There may be a place for the routine use of post-operative vaginal radium prophylactically. In every case a careful and frequent follow-up visit with a speculum examination of the vaginal vault is essential to recognize these common recurrences at the earliest possible moment, as they are frequently extremely radiosensitive.

Finally with carcinoma of the endometrium, as opposed to the cervix, there is no doubt that surgery gives better results than does radium.

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Dr. J. Bamforth (St. Thomas's Hospital): My contribution concerns chiefly those cases described by Mr. Rickford which were treated at St. Thomas's Hospital. Pathological sections from 76 have been examined and these constitute practically all the cases of this condition admitted for treatment during the period January 1, 1943, to March 31, 1952. It is unfortunate that in the earlier years of this period, during the war pathological investigations were not so extensive as could be desired. In these circumstances an elaborate classification is impossible and I have therefore divided the cases into four groups.

Adenocarcinoma (Grade 1)	—	14 cases.
Adenocarcinoma (Grade 2)	—	42 cases.
Adenocarcinoma (Grade 3)	—	17 cases.
Squamous cell carcinoma	—	3 cases.

The histological grading of tumours is always open to criticism but in the case of Grade 3 the appearances were so atypical that there was little difficulty.

The necessity for thorough curettage is obvious because it happens in a few cases that only some of the curettings removed for diagnosis are malignant. From time to time also a case occurs in which the curette has apparently removed all traces of the disease because nothing can be found on examination of the uterus after removal.

In the adenocarcinomas of both Grades 1 and 2, one of two different types of cell appears to be concerned. Although there are cases with intermediate types of cell this distinction apparently exists. In the one type the cell is a short columnar cell which stains well and calls to mind the glandular epithelial cells of the normal post-menstrual endometrium. In the other type the cell concerned is a much taller columnar cell which stains less intensely, resembling that seen in endometrial hyperplasia. This condition, which may or may not be accompanied by cystic glandular formations, is considered to be due to the action of the œstrogenic hormone. Considerable attention has been paid during recent years to the frequent occurrence of endometrial hyperplasia both before and especially after the menopause, sometimes after the lapse of many years. Moreover, histological examination reveals that some cases of endometrial hyperplasia show atypical epithelial proliferation. This may be small and localized but often the changes are more extensive and the glands over large areas of endometrium may show atypical changes. In some cases the appearances are such that it is difficult to be sure whether we are dealing with a malignant condition or not. The association of endometrial hyperplasia and adenocarcinoma of the uterine body has been emphasized by a number of authors during recent years. It appears that in most cases a considerable period of time is required for the development of carcinoma in a case of endometrial hyperplasia. It is considered by some authorities, though not by all, that the occurrence of endometrical cancer in cases of feminizing œstrogenic tumours is too frequent for it to be merely a coincidence.

In this series, 14 of the 56 adenocarcinomas of Grades 1 and 2 have been found to be associated with endometrial hyperplasia and almost all are of the large columnar cell type. In a few of these cases areas of actively secreting glandular epithelium have formed part of the malignant tissue.

[illegible] cases have been placed in Grade 3. In some the sections show that a few glands are still present but for the most part these neoplasms are quite undifferentiated. In some the cells are small and round and show a resemblance to sarcoma.

Squamous-cell metaplasia of greater or less degree has been found in the majority of cases from all three grades, even in the most undifferentiated types. It does not appear to have made any difference to the degree of malignancy. 3 cases were classified as squamous cell carcinoma. In none were cell nests found.

Though this series is small, and insufficient time has elapsed to draw definite conclusions, so far as it goes the prognosis appears to be much better with the lower degrees of malignancy. Of the 17 cases in Grade 3, 9 have already died, contrasting with 1 death in the 14 cases of Grade 1, and 5 in the 42 of Grade 2; of the 3 cases of squamous cell carcinoma, only 1 survives.

Dr. M. Lederman (Royal Cancer Hospital): There are several examples in the human body of organs which are functionally highly specialized and anatomically single yet which give origin to cancers of several distinct types. The uterus is one such organ since among its neoplasms at least three forms of cancer can be distinguished, each having its own particular natural history and different prognosis, and each meriting a different treatment policy. The division of uterine cancers into those arising from the cervix (including endocervix) and those arising from the corpus is of very long standing but the possibility that other types exist was appreciated by Heyman as long ago as 1936 and only recently, in 1949, given the attention it merits.

Mr. C. W. A. Kimbell has stressed the system of classification advocated by Heyman and its importance lies in the fact that the treatment a patient receives will depend largely upon the group to which her tumour happens to belong.

I believe very firmly that with certain exceptions, cancer of the cervix is chiefly the province of the radiotherapist: equally, cancers affecting the corpus and cervix I believe are best treated by radiotherapy in the first instance with surgery in reserve. It is this group of cases that provide the radiotherapist with unexpected recurrences or unusual metastases and confound the surgeon who is wedded to the classical panhysterectomy. As far as what one may term "corpus cancer" proper is concerned, there are few who would dispute the surgeon's claim to these cases. The results of surgery are said to be good whilst the technical difficulties of radiotherapy are considerable. However, Heyman in Sweden and the late Mrs. Hurdon and Margaret Tod in this country have shown what careful radiotherapy can offer the early cases of this kind.

Having conceded to the surgeon the operable case of corpus cancer, what part has radiotherapy to play in the treatment of this disease?

Radiotherapy has a threefold part to play:

(1) It can be employed as an adjunct or complement to surgery in the form of pre- or post-operative radiation: (2) it can be used as an alternative to surgery for technically operable cases where the patient is a poor surgical risk, and finally, (3) it can be employed for cases not amenable to surgical treatment such as the inoperable and recurrent case.

Nobody can dispute the importance of radiotherapy to the surgically hopeless case but in this country only a minority of surgeons appreciate the importance of radiotherapy to the successful outcome of surgery. When there is proper and genuine co-operation between the surgeon and radiotherapist, i.e. both see the cases before treatment is embarked upon, it is possible for the radiotherapist to assist the surgeon in two distinct ways:

(1) By pre-operative radiation the surgeon can be helped to overcome some of his difficulties before operating. The indications are: (*a*) the doubtfully operable case; (*b*) spread to the cervix or suggestion of spread outside the uterus; (*c*) the anaplastic lesion.

Pre-operative treatment does not entail giving massive doses of radiation and need not therefore unduly delay operation or add to its technical difficulty.

(2) By post-operative irradiation the surgeon can be helped salvage his mistakes, i.e.

(*a*) incomplete operation (i) lymph nodes or other secondary spread; (ii) involvement of cervix when panhysterectomy has been performed; (iii) rupture and spill.

(*b*) prophylactic treatment.

In contrast to pre-operative irradiation, post-operative treatment for cases where operation has been incomplete must be given to full doses and entails considerable discomforts and certain risks. Prophylactic radiation against vaginal recurrence is, however, a simple procedure to be recommended in certain cases.

Radiotherapy is a valuable alternative to surgery. There is no doubt that radiotherapy can cure *endometrial* adenocarcinomata and in these circumstances, whilst acknowledging the small risks of modern surgery, patients with technically operable tumours who are unfit for operation should not be asked to accept risks which can be avoided by radiotherapy.

Technique.—Curative treatment usually necessitates local radium therapy in some form. There are two main radium techniques:

(1) Modified cervix techniques using a central radium source. These techniques are satisfactory for the early case when the uterus is not grossly enlarged or the seat of fibroids. For the common inoperable case likely to be referred for radiotherapy, techniques of this kind can be preceded by X-ray therapy which helps reduce the bulk of the neoplastic uterus to manageable proportions.

(2) Heyman and others have, however, approached the treatment problem from a different angle, i.e. the single line source is abandoned and the uterine cavity packed with multiple sources. By this means an attempt is made to deliver radiation to all parts of the tumour, irrespective of the size and shape of the uterine cavity.

Heyman with his unique experience and results has firmly established the value of his packing method.

The use of radium as a prophylactic post-operative measure against vaginal metastases has long been advocated by Heyman and recently Mrs. Willmott Dobbie has published some valuable work in this connexion (1953, *J. Obstet. Gynæc., Brit. Emp.*, **60**, 702).

X-ray therapy at the ordinary voltage range, i.e. 200–400 kV, is of limited value in the treatment of pelvic cancer: whether supravoltage X-radiation or the large telecobalt units will have much to offer remains to be seen. X-ray therapy is of most use as a routine *post-operative* measure since by this means the whole pelvis, including the operative field, can receive a thorough general irradiation. X-ray therapy is also the main method of treating advanced inoperable cases where palliation is the sole objective, or in the advanced case showing invasion of the cervix, vagina or parametria; where curative treatment is contemplated X-radiation can be supplemented by local radium treatment, depending on the response obtained.

For the common vault recurrence, X-ray therapy to the pelvis followed by local radium is the treatment of choice, whilst introital deposits are best treated by radium implantation. Metastases outside the pelvis occasionally require treatment, i.e. para-aortic nodes, deposits in the abdominal wall, whilst ascites and pleural effusions can occasionally be helped by injections of radioactive gold.

Mr. W. Hawksworth (Radcliffe Infirmary, Oxford) presented the results of investigation and treatment which had been carried out in the Area Department of Obstetrics and Gynæcology during the past thirteen years on patients with carcinoma of the body of the uterus. In that time, up to the end of April 1954, 184 such patients had been treated and of these 98 more than five years ago.

Several slides were shown which depicted the following:

(1) *Age incidence.*—The commonest age group was between 55–59. 29 women were under 50 years of age, and one was 26. 85% of cases occurred in the post-menopausal years.

(2) 84 or 46% had had no children. The incidence of the disease decreased with increasing parity, but it was demonstrated that carcinoma of the corpus uteri obviously occurred whether a woman had borne children or not.

(3) The menopause had been delayed in 101 or 55% of the cases. 15 were still menstruating regularly at the age of 50 or over.

(4) Irregular post-menopausal bleeding had been present in 120 or 65% of cases. There was no abnormal bleeding in 23 cases, but in all except 3 of these there was a brownish or blood-stained discharge. In other words a varying combination of irregular bleeding and/or blood-stained or brownish discharge had been the rule.

Two cases in the series (one aged 26 and the other aged 37) presented complaining of primary infertility and routine endometrial biopsy showed carcinoma of the corpus uteri.

(5) The uteri in 89 or 48% of the patients had been described as larger than normal, 59 listed as normal, and 23 as smaller than normal.

(6) The state of the cervix was described in the records of 117 cases, and 48 or 41% were recorded as softened.

The diagnosis of carcinoma had been confirmed histologically in 183 of the 184 cases. Over 60% came into Grade II of Broder's classification, and the lowest incidence was in Grade IV.

In this series of cases treatment by operation was considered to be the method of choice. The cervix was packed with gauze and sutured, the vagina was painted with Bonney's blue, and a total hysterectomy and bilateral salpingo-oophorectomy was performed by the abdominal route.

(7) Of 184 patients seen with carcinoma of the body of the uterus 164 were treated by surgical removal as described: operability rate of 89%. There were no operative deaths but 8 patients died within twenty-eight days of operation, a mortality of 4·9%.

During the same period under review, there were in the Area Department of Obstetrics and Gynæcology at Oxford, 1,844 total hysterectomies performed by the abdominal route for various conditions other than carcinoma of the uterine body, and in this group the post-operative mortality was only 0·8%.

The reasons for the difference in post-operative mortality are obvious, in that these patients with cancer are often frail, poor operative risks, and belong to an older age group.

(8) *Five-year results.*—98 patients had been seen more than five years ago between 1939 and December 1948; all but 2, who cannot be traced, have been followed up. The absolute five-year survival rate in the series was 59%.

In the series of 98 patients seen for the first time more than five years ago, 87 were submitted to radical surgery. It was found that 69 of these had no evidence of spread beyond the uterus at the time of operation and in this group 10 (including 2 untraced) = 14·5%, died within five years of recurrence of carcinoma. There were, however, among these 69 cases, 4 post-operative deaths and 4 deaths from intercurrent disease, giving a five-year survival rate in this group of 74%. There were, on the other hand, 18 cases out of the 87 operated upon, who at the time of operation had evidence of spread beyond the uterus, demonstrated either in the gross or on histological examination. In this group of 18 patients, 13 (or 72%) died within five years of recurrence of

carcinoma. There were no post-operative deaths, giving a five-year survival rate in this group of only 28% as compared with 74% in the former group.

It is obvious from these figures that the surgical treatment of carcinoma of the body of the uterus offers the best chance of cure when there is no extensive spread of the growth. Although this series is small, it serves to emphasize strongly the importance of early diagnosis and the possibilities of surgical treatment.

Mr. Robert Percival demonstrated the cervical occlusive clamp that he had devised two years ago, for temporarily compressing the cervix during hysterectomy for carcinoma of the body. It was not meant to take the place of prophylactic irradiation in conjunction with the operation but rather to aid in preventing spread of growth due to spill, not only in the pelvis but elsewhere in the peritoneal cavity. It did also, of course, prevent the escape of infected material.

Cervical occlusion by means of suturing or packing was common practice yet it was not a cell-tight or watertight closure, and in the nullipara was often a difficult and time-consuming operation. This clamp was almost as quickly applied to the cervix as a volsella, and proof of its efficiency had been demonstrated many times during hysterectomy for benign conditions, using intra-uterine dye.

The clamp unit was made up of two separate parts: (1) A pair of strong, light, carrier or application forceps with which to apply the clamp to the cervix and to effect its firm compression. (2) The small sharp-toothed clamp itself, automatically locking on compression and remaining on the cervix when the carrier forceps was slipped off. In this position it took up very little room in the vault and in no way interfered with the hysterectomy. In fact it acted as a very convenient landmark which identified the base of the portio vaginalis. (Here a detailed description of the clamp unit was given using lantern slides. *See Lancet*, 1952, ii, 810.)

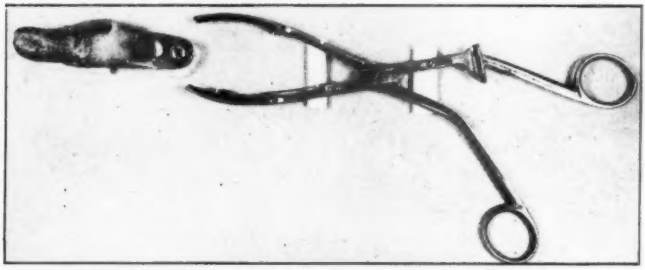

FIG. 1.—Cervical occlusive clamp and carrier forceps.

Dr. Paul Strickland (Mount Vernon Hospital, Northwood) described a flexible intrauterine applicator, loaded with radioactive cobalt (Co^{60}) in the treatment of carcinoma of the uterine body. The apparatus consisted of a steel spring loaded with multiple small sources of radioactive cobalt, with inert steel pellets between them. At the fundal end of the applicator, six contiguous cobalt sources were used. Each source had a strength of 2·8 mc. and, in an average case, 74 mc. were required. This delivered a dose of 6,000 r to a plane 1·5 cm. away from the applicator in 2 insertions of thirty hours or so, separated by an interval of a week (Jones, 1952).

After dilatation of the os, the cervix tube was inserted. The loaded spring was passed through the tube and opened out to assume accurately the shape of the uterine cavity. The ends of the spring fitted tightly into a drilled brass cylinder which rested in the cervical canal. The cylinder and cervix tube were kept in position by a brass plug and key (Fig. 1).

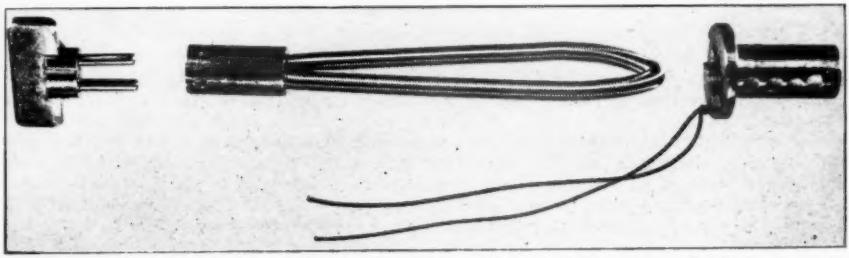

FIG. 1.—Intrauterine cobalt applicator showing brass plug and key on left, spring and cylinder in centre and cervix tube on right.

The apparatus was removed without anæsthesia.

Since 1950, 15 cases had been treated. So far, none had recurred locally. It would seem that this radical radiotherapeutic technique had a place in the management of those cases of carcinoma of the uterine body considered unsuitable for operation, particularly if there was no clinical evidence of spread to the parametria. This method did not deliver an adequate dose of radiation to the vaginal vault, and though no recurrences had yet been encountered there in this series, additional radium sources would be needed for vaginal insertion. The treatment did not upset the patient and there had been no radionecroses. (Strickland, 1953).

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Mr. H. Arthure said that he intended to use the cervical clamp described by Mr. Percival. He had no doubt that surgery was the treatment of choice in carcinoma corporis, but he believed that the risk of a recurrence in the vaginal vault could be minimized by a preliminary Stockholm dose of radium, one or two weeks before operation, in order to destroy superficial cancer cells. He had been using this method since 1947 without preliminary suture of the cervix, and had not so far seen a vaginal recurrence. A Wertheim hysterectomy must be performed if involvement of the cervix was suspected, otherwise total hysterectomy and removal of the appendages should be sufficient.

Mr. Anthony Green (Royal Northern Hospital, London):

Demonstration of Treatment Methods in use and a New Method of Employing Radioactive Tantalum in a Balloon

The methods in use were divided into:

(1) *Those methods which irradiate the uterus satisfactorily in the lateral plane only.* These are (*a*) The Marie Curie Hospital method (Hurdon, 1942) employing a central radium tube and 2 cornual applicators; (*b*) Y-shaped radium applicator: the 2 limbs of the Y go up in the direction of the cornua (Schmitz *et al.*, 1952); (*c*) The new Mount Vernon Hospital method (Jones, 1952). A radioactive cobalt loop occupies the fundus and lateral walls.

With these methods it is not possible to obtain adequate radiation in the antero-posterior plane in a large uterus without giving a very high intrauterine dose and taking a risk of *late* necrosis.

The five-year results where available, (*a*) and (*b*), are inferior to those below.

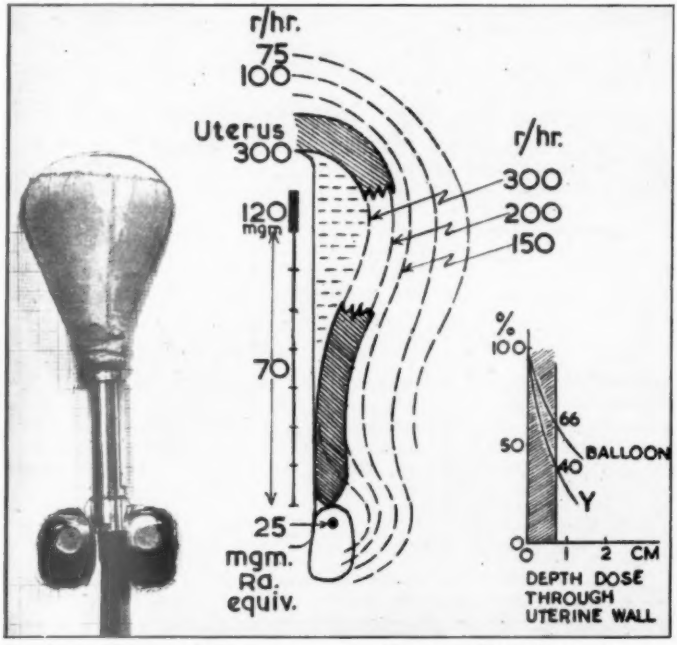

FIG. 1.—A, Treatment balloon. FIG. 1.—B, Dose charts.

(2) *Those methods which aim at filling the uterus in all directions with an irradiator.*

(*a*) *Stockholm method* (Heyman) by which the emptied uterus is filled with radium capsules has produced the best results—74% (5 years) in clinically operable cases—(Kottmeier, 1953).

(*b*) *Balloon method* (Green). This consists of a balloon containing a central radioactive tantalum source (Ta^{182}) and when distended there is uniform irradiation in all directions. The method of selection of the correct balloon diameter and length irradiated by means of a measure was demonstrated. The appliance is inserted through the os by a miniature "rectal" speculum and distended with weak Uriodone (radio-opaque I.V.P. solution). The distension is limited by a strong silk cover. On the same length of tubing is a rubber indicator balloon (later strapped to the patient's thigh) which proves that the intrauterine balloon is distended (Figs. 1, 2A, 2B, 3).

A

B

FIG. 2.—Radiographs showing: 2A, Radioactive tantalum in balloon. 2B, Shape of blackening on film.

FIG. 3.—Apparatus in patient.

Results.—Earlier cases were treated with a pseudo-balloon by wrapping latex sheet around the radium in the fundus in order to imitate the balloon method. The patients treated were in the main considered inoperable by their gynæcologists.

9 cases—7 alive—5 symptom free for five years or more.
2 recently treated but locally well.
2 dead—1 generalized abdominal metastases.
1 presumed dead (lost to follow-up).
Operative mortality: 0. Morbidity: transient diarrhœa in some.

Details of treatment of these cases were given. The total dosage was 6,000 to 8,000 r given in 2 doses 1 cm. beyond the outside of the balloon, i.e. peritoneal surface of uterus.

The demonstration also showed the flexibility of an empty malignant uterus in both dimensions as well as its strength under tension by the use of attached weights. Spring-mounted cornual irradiators combined with a central radioactive source were shown as one of the methods available for treating the small flat uterus.

Future.—Schmitz has shown that using pre-operative irradiation with the Y applicator there is a 65% survival but this rises to 86% of cases when the uterus has no viable cancer remaining. It follows that any method of treatment, e.g. balloon, which may increase the number of cancer-free cases has a possibility of increasing the five-year survival rate in the direction of 86%.

Thanks are due to Miss Fisher, B.Sc., for the excellent dose curves, to Mr. B. A. Spicer for so ably providing the apparatus, and to the School of Stitchery and Lace for the silk covers.

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[*April* 23, 1954]

DISCUSSION ON LEUCOPLAKIA AND ALLIED CONDITIONS [*Abstract*]

Mr. C. M. Gwillim: In March 1944 Mr. V. Bonney addressed this Society on this subject and appealed to dermatologists to clear up a depressing muddle. It seems to me that a confusion of words and classifications is the root of our trouble.

The term "leucoplakia" was introduced by Schwimmer in 1877 to mean white patches on *mucous surfaces only*. This type of leucoplakia may occur in the vulva but in my experience it is very rare, as an isolated entity and without spread outside the mucous surfaces. Wallace and Whimster state "leucoplakia confirmed histologically has not been observed outside the inner aspects of the labia majora, perianal area, or the genito-crural folds". I have seen it associated with cancer in all these places.

The term "kraurosis" was introduced by Breisky in 1885 to describe a white contracted atrophic vulva. It has been used to describe three different conditions; a white contracted vulva, a red contracted vulva, and a condition of atrophy limited to the vestibule. Berkeley and Bonney used it to describe an atrophic condition primarily of the vestibule, and only secondarily associated with atrophy of the vulva and vagina. There is a condition which is due to excessive atrophy from œstrin deficiency. This atrophy shows first around the urethra. Atrophy of the vagina and vulva may also occur. The symptoms can be cured rapidly by stilbœstrol. In fact, I consider this clinical test to be diagnostic.

Other authors have thought that kraurosis describes the terminal phases of lichen planus, lichen sclerosus vel atrophicus, leucoplakic vulvitis, primary atrophy of the vulva, senile atrophy.

On November 11, 1909, Berkeley and Bonney described "leucoplakic vulvitis". Stress was placed on the fact that the condition was not limited to the inner aspects of the vulva. The classification was justified as a means of separating this condition from kraurosis, as just described, and to emphasize the need to treat by excision a precancerous condition, but it has been under constant attack from the dermatologists.

Wallace and Whimster (1951) classify vulval atrophy into four types. Three have the following features in common: None of them responds to any treatment other than excision. They all tend to become malignant.

Dr. R. T. Brain said in 1944: There is a condition of the vulva with whitish thickened rough horny patches, representing hyperplasia of the epithelium. It is pre-cancerous, and associated with senile keratosis. Perhaps a better name for it is leucokeratosis. The condition Bonney describes as leucoplakic vulvitis is leucokeratosis, but some of his clinical and histological observations certainly apply to lichen planus and lichen sclerosus."

A classification is justified by its usefulness and Bonney was stressing the importance of a clinical entity, cured only by excision, and extremely prone to malignant change. It is essential to stress this tendency.

To sum up: My aim in opening this discussion is

(1) To discuss our muddled nomenclature;

(2) to invoke the aid of dermatologists and histologists in an attempt to clarify it;

(3) and, as a clinician, to stress the value of Bonney's contribution in describing leucoplakic vulvitis—whether it be three conditions which come to a common end, or one condition which might be called leucokeratosis—for the clinical entity must be treated with the seriousness it deserves, and not too long with the placebo of the moment, whether it be hormone or unguent.

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WALLACE, H. J., and WHIMSTER, I. W. (1951) *Brit. J. Derm.*, **63,** 241.

Dr. H. J. Wallace: A number of classifications of the various forms of vulval atrophy and leucoplakia have been proposed. It is suggested that owing to discrepancy in nomenclature and to inadequate joint study of these disorders by gynæcologists and dermatologists some confusion still obtains. Most of the confusion appears to derive from varying conceptions of the term kraurosis and to a slightly lesser degree from ignorance about the existence of an atrophic form of scleroderma—so-called lichen sclerosus which not infrequently occurs on the vulva and perianal area. The confusion with regard to the term kraurosis appears to be greater in this country than on the Continent or in America where the term kraurosis has always been and is still used to describe a clinical entity entirely different from the disorder subsequently described under this name in most British textbooks on gynæcology. It is suggested that apart from the common skin disorders such as dermatitis and psoriasis there are three and possibly four distinct entities which may give difficulty in differential diagnoses.

(1) *Primary atrophy of the vulva*, alias kraurosis, as originally described by Breisky in Germany and later by Jayle and Darier in France as a sclerosing progressive atrophy of the muco-cutaneous integument of the vulva. After a varying period the disorder is often complicated by leucoplakia and carcinoma.

(2) *Lichen sclerosus*—an atrophic form of scleroderma which may occur anywhere on the body but frequently affects the vulva and perianal area, and is unrelated to lichen planus. On the vulva but in no other area lichen sclerosus may undergo leucoplakic and subsequently cancerous change.

(3) *Leucoplakia*—which may occur apparently *de novo*, sometimes apparently following chronic neurodermatitis, but most frequently complicating primary atrophy or lichen sclerosus.

(4) *Senile genital atrophy*—of little clinical significance with regard to symptoms or the risk of cancer. It is presumably to this entity that the term kraurosis has been applied in this country, albeit but vaguely.

Dr. Magnus Haines subdivided leucoplakia and allied conditions of the vulva into (*a*) kraurosis, (*b*) a non-leucoplakic group associated with an assorted terminology and not necessarily tending to become carcinoma, (*c*) leucoplakia which is premalignant, (*d*) pre-invasive carcinoma. Kraurosis is a clinical diagnosis and is considered by many to respond to treatment readily and even permanently. In his study of non-leucoplakic vulvitis all those cases due to specific agents were excluded. Causes such as contact dermatitis, diabetes and fungus infections were common. The list were varied according to geographical and other circumstances, e.g. nutrition. Leucoplakia was considered both as an entity and in its association with carcinoma. Three case histories were given. Carcinoma *in situ* of the vulva was not a new disease ; though it appeared to be uncommon. Its relation with carcinoma elsewhere was considered. Bonney (1938, 1944) in later years drew a distinction between leucoplakia and other conditions, not including kraurosis.

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Professor H. McLaren, Mr. Charles D. Read, Mr. Oswald Lloyd and **Mr. Stanley A. Bond** also spoke.

[*May* 28, 1954]

PATHOLOGICAL MEETING

Dr. D. L. Phillips and Dr. J. S. Scott : Seven cases were described of Behcet's syndrome of recurrent genital and oral ulceration (Figs.1–4) associated with lesions of the anterior chamber of the eye. The cases all occurred in the reproductive period and presented at gynæcological clinics on

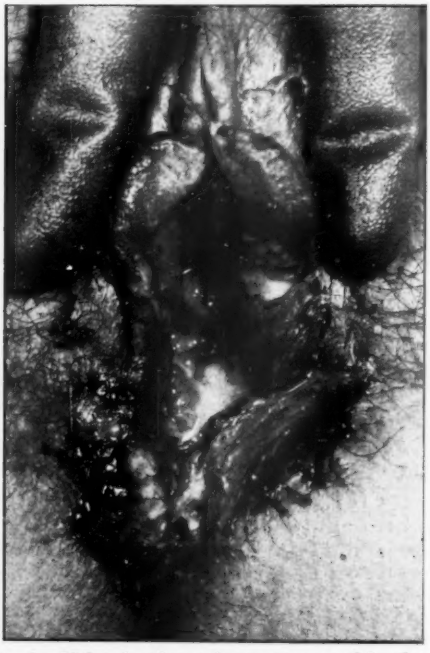

FIG. 1.—Vulva showing early appearances of the ulcer.

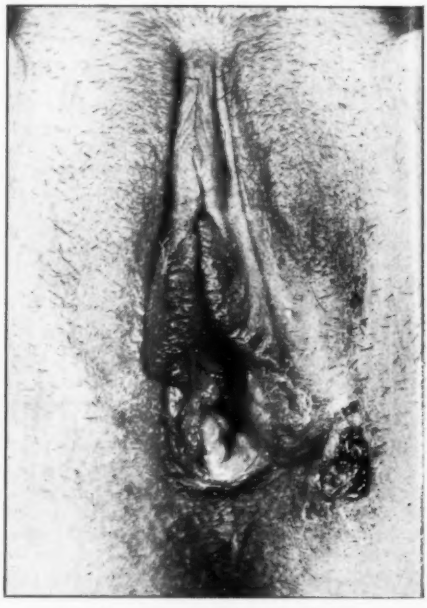

FIG. 2.—Vulva showing ulcer healing.

account of the incapacitating nature of the lesions. 3 cases had a menstrual periodicity and 2 had irregular menses. 4 cases had eye involvement, 1 being completely blind. 3 cases had joint manifestations and 1 had signs of central nervous system lesions. In 1 case the commencement of the syndrome was preceded by the excision of a laryngeal carcinoma.

Laboratory investigations showed no specific abnormality.

The diagnosis is based upon the recurrent appearance of painful lesions in two of the three sites, other specific causes having been excluded. The genital and oral lesions are identical with those known as ulcus vulvæ acutum, periadenitis mucosa necrotica recurrens and aphthous mucosal ulceration.

FIG. 3.—Tongue showing deep ulcer

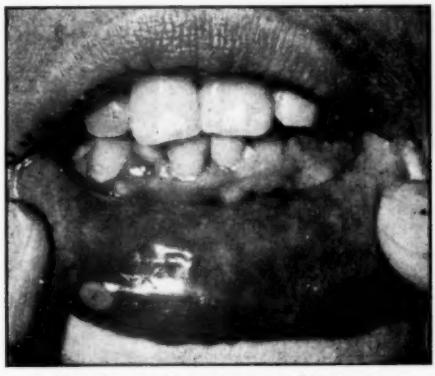

FIG. 4.—Early appearance of lip ulcer.

The ætiology is unknown but it is suggested that it is a "stress" phenomenon.

No treatment used up to the present has had any certain effect. 4 of these cases, however, were treated with cortisone for up to five months without serious recurrence.

The importance of the syndrome lies in the fact that the pain associated with the lesions is often incapacitating; blindness may ensue and death has been recorded; furthermore it is possible that the diagnosis is frequently missed.

[The paper was illustrated with slides.]

Mr. J. D. Bury showed a case of chorioangioma of the placenta in a multiparous patient of 35. The pregnancy was uneventful till the 27th week, when it was noted that she gained abnormally in weight during the preceding 4 weeks. Two weeks later she developed abdominal pain and orthopnœa and the uterus filled the abdomen. Attacks of renal pain occurred with increasing frequency and there was some dilatation of the renal calyces on the right side. Paracentesis uteri was performed because of severe distress and enlarging girth. After 90 oz. was removed uterine contractions occurred and paracentesis was discontinued. The uterus rapidly enlarged again and distress was severe, so at 31 weeks surgical induction was performed by high rupture of the membranes. Ten minutes after this bleeding *per vaginam* occurred 15 oz. Shock was severe and necessitated a blood transfusion. A stillborn infant was delivered four hours later followed by the placenta and 22 oz. of retro-placental clot. The placenta weighed 3 lb. and on one edge was a firm fleshy tumour clothed by amnion and consisting of capillary sinusoids.

130 cases of chorio-angioma have been described in the last 125 years, one-third of which were associated with hydramnios.

Dr. A. N. Horwitz described a case of simultaneous bilateral ectopic pregnancy fulfilling the criteria postulated by Cuthbert Lockyer in 1916. The patient was 26 and had had 3 previous full-term pregnancies. Her last menstrual period was November 15, 1953, and she was operated upon on January 5, 1954. There was free blood in the peritoneal cavity. The right tube was distended by blood but not ruptured. The left tube had ruptured and tubal abortion occurred. Both were approximately the same size and contained similar chorionic villi.

The case bears out the importance of inspecting both tubes in every case of ectopic gestation.

Mr. Charles Flood described 5 cases of primary carcinoma of the fallopian tube—3 in post-menopausal patients who had had a blood-stained vaginal discharge. 4 patients were nulliparous. The duration of symptoms was from ten weeks to eight months. Total hysterectomy and bilateral

salpingo-oophorectomy was performed in all cases and 2 patients were alive fourteen and nineteen months after operation. 3 had died eight, fourteen and fifteen months post-operatively.

Mr. Bruce Eton showed a vaginal calculus removed from a child suffering from incontinence of urine. The possibility of an accessory ureter was suggested.

Mr. E. A. J. Alment described 2 cases of monoamniotic twin pregnancy. The first patient, a primigravida, had a forceps extraction for the first twin, which lived; the second twin was a breech extraction, stillborn. There was no trace of amniotic remnant between the two cords which were knotted.

The second case was also in a primigravida. She had a spontaneous vertex delivery of the first twin, and forceps in the aftercoming head of the second. Both lived. There was no amniotic remnant across the placenta and the cords were not entangled.

In 150 cases described the fœtal survival rate was 49%.

Mr. J. Frankenberg showed a case of slow rupture of the uterus in a patient with four pregnancies and one abortion, who had a curettage for irregular periods in March 1953 followed by a pregnancy in September 1953, during which she bled irregularly until November 1953. During this period she developed a complete afibrinogenæmia—due to prolonged bleeding. This was treated by very large doses of fibrinogen and blood transfusions.

She developed signs of accidental hæmorrhage and later those of a ruptured uterus. She passed a stillborn fœtus and placenta *per vaginam* before laparotomy was performed which revealed a rupture of the uterus in the left broad ligament. A total hysterectomy was performed and the patient eventually made a complete recovery.

The slow rupture may have been caused at the time of the curettage and the fibrinogen store was used up in the endeavour to plug the gap in the uterus. Supplies of fibrinogen were generously given by the Netherlands and United States and are now available in the Lister Institute and St. James's Hospital, London.

Miss J. M. Clements described a case of carcinoma of the fallopian tube associated with bilateral tuberculous salpingitis and uterine fibroids, in a nulliparous married woman of 43 with menorrhagia.

A total hysterectomy and bilateral salpingo-oophorectomy was performed. The left fallopian tube showed fibrocaseous tuberculosis and a primary carcinoma. The right tube showed fibrocaseous tuberculosis and the uterus had multiple fibroids. The ovaries were normal.

Mr. R. M. Feroze described a case of primary bilateral carcinoma of Bartholin's gland in a married multiparous woman of 55 with post-menopausal hæmorrhage. There was one palpable inguinal lymph node on the right side which contained squamous cell carcinoma. Curettings were normal. Radical vulvectomy and bilateral ilio-inguinal lymphadenectomy were performed in two stages. Both Bartholin's glands contained squamous cell carcinoma.

Five months later the patient was well and free from recurrence.

Dr. P. E. Hughesdon showed a case of adenomatoid tumour of the uterus. The patient was a married woman (aged 47, para 2, one year post-menopausal), complaining of five years' left abdominal pain and two years' dyspareunia. The only positive finding was a bulky tender retroverted uterus, removed, with both adnexæ, two days after admission: convalescence was uneventful. Fused with the left cornual uterine wall and adjacent round ligament was a walnut-sized knob resembling a fibroid: it projected into the broad ligament with a few small subperitoneal vesicles overlying it. *Microscopically*, it consisted of muscle bundles interspersed with groups and trains of close-packed acini of varied size and shape (*see* Fig. 1), having either a cubical epithelial or an endothelioid lining. Lumina were empty save for a little mucus and desquamated cells. The intervening tissue showed lymphocytic collections, some with germinal centres. Dr. Hughesdon said his thanks were due to Mr. I. S. Robertson Bain and Dr. Michael Aldridge for permission to present this case.

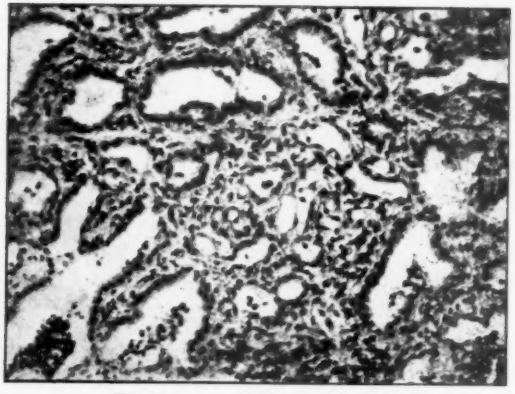

FIG. 1 × 120 (H. and E.)